

SAJOUS'S ANALYTIC CYCLOPEDIA OF PRACTICAL MEDICINE

CHARLES E. de M. SAJOUS, M.D., LL.D., Sc.D.

ASSISTED BY

LOUIS T. de M. SAJOUS, B.S., M.D.

WITH THE ACTIVE CO-OPERATION OF OVER

ONE HUNDRED ASSOCIATE EDITORS

NINTH REVISED EDITION

**Illustrated with Full-page Half-tone and Color Plates
and Appropriate Cuts in the Text**

VOLUME TWO



PHILADELPHIA
F. A. DAVIS COMPANY PUBLISHERS

1923

COPYRIGHT, September, 1922
BY

F. A. DAVIS COMPANY

Copyright, Great Britain. All Rights Reserved

PRINTED IN U. S. A.
PRESS OF
F. A. DAVIS COMPANY
PHILADELPHIA, PA.

CONTRIBUTORS TO VOLUME II.

RUDOLPH MATAS, M.D.,

Professor of Surgery, Tulane University,
NEW ORLEANS, LA.

FRANCIS X. DERCUM, M.D.,

Professor of Nervous and Mental Diseases, Jefferson Medical College,
PHILADELPHIA, PA.

JAMES M. ANDERS, M.D., LL.D.,

Professor of Medicine, University of Pennsylvania Graduate Medical School,
PHILADELPHIA, PA.

SOLOMON SOLIS-COHEN, M.D.,

Professor of Clinical Medicine, Jefferson Medical College,
PHILADELPHIA, PA.

ERNEST LAPLACE, M.D., LL.D.,

Professor of Surgery, University of Pennsylvania Graduate Medical School,
PHILADELPHIA, PA.

N. S. DAVIS, JR., M.D.,

Professor of Medicine, Northwestern University,
CHICAGO, ILL.

WILLIAM B. COLEY, M.D.,

Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University,
NEW YORK CITY.

GUTHRIE McCONNELL, M.D.,

Formerly Professor of Pathology, Bacteriology and Hygiene, Temple
University Medical School,
PHILADELPHIA, PA.

E. D. BONDURANT, M.D.,

Professor of Mental and Nervous Diseases, University of Alabama School of Medicine,
MOBILE, ALA.

WILLIAM S. GORDON, M.D.,

Professor of Medicine and Clinical Medicine, University College of Medicine,
RICHMOND, VA.

COPYRIGHT, September, 1922

BY

F. A. DAVIS COMPANY

Copyright, Great Britain. All Rights Reserved

CONTRIBUTORS TO VOLUME II.

RUDOLPH MATAS, M.D.,
Professor of Surgery, Tulane University,
NEW ORLEANS, LA.

FRANCIS X. DERCUM, M.D.,
Professor of Nervous and Mental Diseases, Jefferson Medical College,
PHILADELPHIA, PA.

JAMES M. ANDERS, M.D., LL.D.,
Professor of Medicine, University of Pennsylvania Graduate Medical School,
PHILADELPHIA, PA.

SOLOMON SOLIS-COHEN, M.D.,
Professor of Clinical Medicine, Jefferson Medical College,
PHILADELPHIA, PA.

ERNEST LAPLACE, M.D., LL.D.,
Professor of Surgery, University of Pennsylvania Graduate Medical School,
PHILADELPHIA, PA.

N. S. DAVIS, JR., M.D.,
Professor of Medicine, Northwestern University,
CHICAGO, ILL.

WILLIAM B. COLEY, M.D.,
Professor of Clinical Surgery, College of Physicians and Surgeons, Columbia University,
NEW YORK CITY.

GUTHRIE McCONNELL, M.D.,
Formerly Professor of Pathology, Bacteriology and Hygiene, Temple
University Medical School,
PHILADELPHIA, PA.

E. D. BONDURANT, M.D.,
Professor of Mental and Nervous Diseases, University of Alabama School of Medicine,
MOBILE, ALA.

WILLIAM S. GORDON, M.D.,
Professor of Medicine and Clinical Medicine, University College of Medicine,
RICHMOND, VA.

CONTRIBUTORS TO VOLUME II.

EDWARD JACKSON, M.D.,

Professor of Ophthalmology, University of Colorado School of Medicine,
DENVER, COLO.

A. PARKER HITCHENS, M.D.,

Major, U. S. Army and Professor in the U. S. Army Medical School,
WASHINGTON, D. C.

HENRY H. JANEWAY, M.D.,

Assistant Attending Surgeon to the City Hospital; Member of the Cornell University
Medical College Commission for Cancer Research,
NEW YORK CITY.

ALFRED GORDON, M.D.,

Neurologist to the Mount Sinai, Northwestern General, and Douglass Memorial Hospitals,
PHILADELPHIA, PA.

WM. BROADDUS PRITCHARD, M.D.,

Professor of Neurology, New York Polyclinic Medical School,
NEW YORK CITY.

JOSEPH COLLINS, M.D.,

Professor of Diseases of the Mind and Nervous System, New York Post-Graduate
Medical School and Hospital,
NEW YORK CITY.

E. G. ZABRISKIE, M.D.,

Adjunct Professor of Diseases of the Mind and Nervous System, New York
Post-Graduate Medical School and Hospital,
NEW YORK CITY.

PERCIVAL NICHOLSON, M.D.,

ARDMORE, PA.

C. E. DE M. SAJOUS, M.D., LL.D., Sc.D.,

Professor of Endocrinology, University of Pennsylvania Graduate Medical School,
and of Therapeutics, Temple University Medical School,
PHILADELPHIA, PA.

L. T. DE M. SAJOUS, B.S., M.D.,

Associate Professor of Pharmacology in Temple University Medical School and
Instructor of Endocrinology in the University of Pennsylvania
Graduate Medical School,
PHILADELPHIA, PA.

CONTENTS OF SECOND VOLUME.

	PAGE		PAGE
Anorexia Nervosa	1	Aphasia (<i>continued</i>)	
Definition	1	Diagnosis	46
General Considerations	1	Word-deafness	46
Symptoms	2	Word-blindness	46
Treatment	7	Aphasia, or Aphemia	46
Anthrax	11	Agraphia	47
Definition	11	Infracortical Motor Aphasia	47
Symptoms	12	Etiology	47
Ascoli Reaction	13	Pathology	49
Etiology	13	Motor Aphasia	49
Prognosis	15	Agraphia	51
Prophylaxis	16	Sensory Aphasia	51
Treatment	17	Prognosis	52
Antimony	20	Treatment	52
Properties	20	Apiol	54
Dose	20	Dose	54
Preparations	20	Physiological Action	54
Modes of Administration	20	Therapeutics	54
Incompatibilities	20	Apocynum	55
Contraindications	20	Preparations and Dose	55
Physiological Action	20	Physiological Action	55
Local Effects	20	Poisoning	56
General Effects	21	Therapeutics	56
Absorption and Elimination	22	Apomorphine	57
Untoward Effects and Acute Poisoning	22	Properties	58
Treatment of Acute Antimonial Poisoning	23	Dose	58
Chronic Poisoning	23	Modes of Administration	58
Therapeutics	24	Incompatibilities	58
Antipyrin	27	Contraindications	58
Properties	27	Physiological Action	59
Dose	27	Apomorphine Poisoning	60
Modes of Administration	28	Treatment	60
Incompatibles	28	Therapeutics	61
Contraindications	29	Appendicitis	64
Physiological Action	29	Definition	64
Acute Poisoning	36	Acute Appendicitis	64
Treatment	37	Symptoms	64
Chronic Poisoning	37	Children	72
Treatment	37	Bastedo Sign	74
Therapeutics	37	Diagnosis and Complications	74
Anus, Diseases of. See Rectum and Anus, Diseases of.		Etiology	80
Aphasia	43	Pathology	87
Synonyms	43	Prognosis	91
Definition	43	Medical Treatment	93
Varieties	43	Surgical Treatment	100
Symptoms	43	Remote Abscesses	106
Motor Aphasia (Aphemia)	43	Subphrenic Abscess	108
Agraphia	44	Diffuse Abscess	109
Amimia	44	Chronic (Relapsing, or Recurrent) Appendicitis	109
Sensory Aphasia	44	Symptoms	109
Auditory Aphasia	44	Prognosis	114
Word-blindness (Alexia)	45	Treatment	114
Subcortical Word-blindness	46	After-treatment of the Various Forms	116
Apraxia	46	Aristol	117
		Preparations	117
		Therapeutics	117

	PAGE		PAGE
Arnica	117	Ascites (<i>continued</i>)	
Preparations	117	Angioneurotic Edema	201
Physiological Action	117	Definition	201
Therapeutic Uses	117	Symptoms	201
Arsacetin. See Atoxyl.		Etiology	202
Arsenic	118	Paroxysmal Form	202
Properties	118	Prognosis	203
Preparations and Dose	118	Treatment	203
Modes of Administration	119	Edema Neonatorum	203
Incompatibilities	120	Idiopathic or Essential Dropsies of	
Contraindications	120	Childhood	204
Physiological Action	120	Treatment	206
Local Effects	120	Asphyxia. See Resuscitation.	
General Effects	120	Aspidium (U. S. P.) or Male Fern	207
Absorption and Elimination	125	Preparations and Dose	208
Acute Arsenic Poisoning	127	Physiological Action	208
Diagnosis of Acute Arsenic Poison-		Aspidium Poisoning	209
ing	129	Treatment of Aspidium Poisoning ...	210
Treatment of Acute Arsenic Poison-		Therapeutics	210
ing	130	Aspidosperma. See Quebracho.	
Chronic Arsenic Poisoning	131	Aspiration. See Paracentesis.	
Diagnosis of Chronic Arsenic Poison-		Aspirin, or Acetylsalicylic Acid	212
ing	135	Dose and Modes of Administration ..	212
Treatment of Chronic Arsenic Poison-		Physiological Action	213
ing	136	Aspirin Poisoning	214
Therapeutics	136	Treatment of Aspirin Poisoning	215
Arsenophenyglycin. See Atoxyl.		Therapeutics	216
Arterial Pressure and Blood-Pressure.		Asteatosis, or Xerosis	218
See Blood-Pressure.		Treatment	218
Arteriosclerosis	143	Asthma	218
Definition	143	Definition	218
Symptoms	143	Symptoms	218
Diagnosis	160	Diagnosis	222
Etiology	163	Etiology and Pathology	224
Pathology	167	Prognosis	228
Treatment	176	Treatment	228
Arthritis. See Joints, Diseases of.		Astigmatism	243
Asafetida	184	Definition	243
Preparations and Doses	184	Irregular Astigmatism	243
Physiological Action	184	Definition	243
Therapeutic Uses	184	Symptoms	244
Ascaris Lumbricoides. See Parasites,		Etiology	244
Diseases Due to.		Treatment	244
Ascites	184	Regular Astigmatism	245
Edema	184	Definition	245
Definition	184	Symptoms	245
Etiology and Pathogenesis	184	Etiology	245
Epidemic Dropsy of India	188	Diagnosis	246
Pathologic and Microscopic Anat-		Treatment	246
omy	189	Athetosis	246
Nature of the Fluid of Edema ...	189	Definition	246
Results of Edema	189	Pathology	249
Starvation Edema	190	Diagnosis	250
Treatment	190	Atoxyl, or Sodium Arsanilate	250
Ascites	192	Dose and Modes of Administration ..	251
Definition	192	Physiological Action	251
Symptoms	193	Untoward Effects and Poisoning ...	251
Diagnosis	193	Therapeutic Uses	254
Pathology	193	Arsacetin	256
Treatment	194	Physiological Action	256
Chylous Ascites	198	Therapeutic Uses	256
Symptomatology	198	Arsenophenyglycin	257
Diagnosis	198	Atropine. See Belladonna.	
Etiology and Pathology	199	Auricular Fibrillation. See Heart and	
Prognosis	200	Pericardium, Diseases of.	
Treatment	200	Autointoxication and Acidosis	257

	PAGE		PAGE
Autointoxication and Acidosis (<i>continued</i>)		Bacterial Vaccines, Prophylaxis and Therapeutics, Staphylococcus (<i>continued</i>)	
Autointoxication	257	Sycosis	367
Definition	257	Periostitis and Osteomyelitis	368
Pathogenesis	258	Prevention in Surgical Work	368
Symptomatology and Diagnosis	259	Colon Bacillus Infections	368
Treatment	260	Meningococcus	374
Acidosis or Acid Intoxication	262	Bacillus Pyocyaneus	375
Etiology	262	Micrococcus Neoformans	376
Symptomatology	263	Tuberculin	377
Diagnosis	264	Kinds of Tuberculin	378
Prophylaxis	266	The Diagnostic Reactions	379
Treatment	267	The Cutaneous Reaction	380
Autoserotherapy. See Ascites, Treatment of.		Characteristic Cutaneous Reaction	381
Aviators' Sickness	268	The Moro Reaction	382
Symptoms	268	Therapeutic Uses of Tuberculin	383
Etiology	269	Leprosy	389
Pathology	269	Diphtheria	390
Prophylaxis	270	Schick Test	392
Bacterial Vaccines	272	Treatment	393
History	272	Diphtheria-bacillus Carriers	394
Theories of Immunity	277	Acute and Chronic Infections of the Respiratory Passages	395
The Phagocytic Theory of Metchnikoff	278	Hay Fever	400
The Theory of Ehrlich	279	Acne	401
The Theory of Metchnikoff	281	Pertussis	408
Technique of the Opsonic Index	282	Asiatic Cholera	410
Opsonins	285	Bubonic Plague	411
Bacterial Vaccines	288	Diseases of the Eye	413
Diagnosis	290	Tuberculous Infections	413
Autogenous Vaccines	297	External Infections	414
Prophylaxis and Therapeutics	307	Internal Infections of the Eye	416
Typhoid Fever	308	Oriental Sore	416
Prophylactic Inoculation	308	Malta Fever	417
Paratyphoid Bacilli	323	Dysentery	418
Isolation and Identification of Typhoid Bacilli	323	Glanders	420
Mixed Infections in Typhoid Fever	325	Otitis Media	421
Pneumococcus	327	Pyorrhea Alveolaris	426
Prophylactic Vaccination Against Pneumococcus	332	Lipovaccines	429
Empyema	332	Summary	430
Streptococcus	334	Bacteriuria	431
Local Infections	335	Barium	431
Erysipelas	336	Preparations and Dose	431
Chorea Minor	337	Physiological Action	431
Septicemia and Endocarditis	338	Barium Poisoning	431
Septicemia, Puerperal	340	Treatment	432
Scarlet Fever	342	Therapeutics	433
Rheumatism	343	Belladonna	433
Gonococcus Infections	346	Preparations and Doses	434
Differential Diagnostic Reaction	348	Incompatibles	434
Urethritis	351	Physiological Action	434
Mixed Infections	352	Atropine Poisoning	440
Epididymitis	354	Treatment	441
Gonococic Arthritis	354	Therapeutics	443
Pyosalpinx	358	Benzoin; Benzoic Acid and the Benzoates	452
Vulvovaginitis	359	Preparations and Doses	452
Conjunctivitis	360	Physiological Action	453
Accessory Methods of Treatment	362	Poisoning by Benzoin Preparations	454
Staphylococcus	363	Benzosulphinidum. See Saccharin.	
Dosage	364	Beriberi	456
Staphylococcus Vaccine	365	Definition	456
		Symptoms	456
		Diagnosis	457

	PAGE		PAGE
Beriberi (<i>continued</i>).		Blood-vessels, Injuries of. See Vascular	
Etiology	457	System: Injuries to Blood-	
Pathology	461	vessels.	
Prognosis	462	Blood-vessels, Tumors of	513
Treatment	462	Definition	513
Betanaphthol	465	Varieties	513
Mode of Administration	465	Angiomata, or Hemangiomata	514
Physiological Action	465	General Histology	520
Therapeutic Uses	465	Etiology and Pathogenesis	522
Bismuth	465	Distribution	526
Preparations and Doses	466	Typographic Distribution	528
Physiological Action	466	Head	528
Bismuth Poisoning	467	Neck	531
Treatment of Bismuth Poisoning	471	Breast	531
Therapeutics	472	Upper Extremities	532
Bites, Venomous. See Wounds, Ven-		Lower Extremities	533
omous.		Splanchnic, or Visceral, Angiomata.	534
Black Death. See Plague.		General Diagnosis	536
Black-water Fever. See Malarial		General Prognosis	537
Fevers; also Hemoglobin-		Treatment	538
uria.		Compression Methods	538
Bladder, Diseases of. See Urinary		Superficial Cauterization	539
System, Diseases of.		Cauterization with Fuming Nitric	
Blastomycosis	476	Acid	540
Definition	476	Freezing	541
Symptoms	476	Penetrating, or Interstitial, Cauter-	
Etiology and Pathology	476	ization	543
Diagnosis	477	Agents which act by Coagulation ..	543
Treatment	478	Physical Agents which Excite Tro-	
Blaud's Pill. See Iron.		phic and Nutritive Changes.	546
Bleeder's Disease. See Hemophilia.		X-rays	547
Bleeding. See Venesection.		Radium	547
Blepharitis and Blepharadenitis	478	Surgical Methods	550
Definition	478	Blue Mass. See Mercury.	
Symptoms	478	Boas-Ewald Test-Breakfast. See Acidity	
Etiology	478	of the Gastric Contents,	
Pathology	479	Tests for.	
Prognosis	479	Bones, Diseases of.....	557
Treatment	479	Periostitis	557
Blood-Pressure	484	Symptoms	557
Systolic and Diastolic	484	Pathology	559
Pulse-Pressure	484	Treatment	559
The Importance of Blood-pressure		Osteitis	560
and Conditions to which it		Etiology and Pathology	560
Applies	484	Treatment	561
Historical	485	Osteitis Deformans (Paget's Disease) .	562
Methods of Measuring Blood-pres-		Treatment	563
sure	486	Osteomyelitis	564
Choice of an Instrument	489	Symptoms	564
The Basis of Blood-Pressure	492	Etiology and Pathology	565
Physiological Variations in Blood-		Treatment	567
pressure	494	Rachitis	570
Blood-pressure in Disease	498	Symptoms	570
Hypertension	498	Etiology and Pathology	571
Diseases with Hypertension	500	Treatment	573
Therapeutics of Hypertension	505	Osteomalacia (Mollities Ossium)	576
Hypotension	507	Symptoms	576
Treatment of Hypotension	513	Diagnosis	576
Blood Transfusion. See Venesection.		Etiology	576
Blood-vessels, Diseases of. See various		Pathology	577
diseases of this class:		Treatment	578
Aneurism, Arteriosclerosis,		Fragilitas Ossium	580
etc., and Vascular System,		Etiology	580
Diseases of.		Treatment	581
		Bone Tuberculosis	581
		Symptoms	581

	PAGE		PAGE
Bones, Diseases of, Bone Tuberculosis (continued).		Bronchitis, Acute, Subacute, and Chronic	660
Diagnosis	582	Definition	660
Etiology and Pathology	582	Symptoms	660
Treatment	583	Chronic and Subacute Bronchitis ..	663
Tumors	587	Dry Bronchitis	664
Bone-Marrow. See Animal Extracts.		Bronchorrhea	664
Boric Acid. See Boric Acid.		Purulent Chronic Bronchitis	664
Borax. See Boric Acid.		Putrid Bronchitis	665
Boric Acid	588	Diagnosis	666
Preparations and Dose	589	Etiology	667
Incompatibles	589	Pathology	670
Physiological Action	589	Prophylaxis	672
Poisoning by Boric Acid and Sodium Borate	590	Treatment	673
Toxic Effects of Boric Acid as a Food Preservative	591	Treatment of Chronic Bronchitis	680
Therapeutics	596	Bronchiectasis	686
Boric Acid	596	Symptoms	686
Sodium Borate; Sodium Biborate; Borax	597	Pathology	687
Sodium Borate Poisoning	597	Treatment	689
Toxic Effects of Sodium Borate (Borax) as Food Preserva- tive	598	Bronchitis, Capillary. See Broncho- pneumonia.	
Therapeutics	599	Bronchitis, Fibrinous, Plastic, or Mem- branous	691
Bright's Disease	600	Symptoms	691
Acute Nephritis, or Acute Parenchy- matous Nephritis	600	Etiology and Pathology	692
Definition	600	Treatment	692
Symptoms	600	Bronchopneumonia	693
Diagnosis	605	Synonyms	693
Etiology	605	Definitions	693
Pathology	610	Varieties	693
Prognosis	612	Symptoms	693
Treatment	614	Diagnosis	695
Chronic Exudative Nephritis, or Chronic Parenchymatous Nephritis	622	Lobar Pneumonia	696
Definition	622	Tuberculous Bronchopneumonia ..	697
Symptoms	622	Influenza	699
Etiology	629	Bacteriology	700
Pathology	629	Morbidity Anatomy	701
Prognosis	631	Treatment	702
Treatment	632	Rachis	712
Non-Exudative Chronic Nephritis, or Chronic Interstitial Ne- phritis	636	Preparations and Dose	712
Definition	636	Physiological Action	712
Symptoms	636	Therapeutic Uses	712
Etiology	640	Buerger's Disease (Thromboangiitis oblit- erans)	712
Pathology	642	Bulbar Paralysis	713
Prognosis	645	Acute Bulbar Paralysis	713
Treatment	645	Symptoms	713
Brill's Disease. See Typhus.		Diagnosis	713
Bromine and Bromides	651	Etiology and Pathology	713
Preparations and Dose	651	Treatment	714
Incompatibles	652	Chronic (Progressive) Bulbar Paral- ysis, or Labioglossolaryn- geal Paralysis	714
Modes of Administration	653	Symptoms	714
Physiological Action	653	Diagnosis	716
Bromide Poisoning	655	Etiology	716
Bromism or Chronic Bromine Poison- ing	657	Pathology	716
Treatment of Bromine Poisoning	658	Prognosis	717
Therapeutics	658	Treatment	717
		Bunion. See Tendons; Bursitis.	
		Burns. See Skin, Surgical Diseases of.	
		Butyl Chloral Hydrate. See Croton Chloral.	
		Cacodylic Acid and Cacodylates	717
		Dose and Modes of Administration ..	718

	PAGE		PAGE
Cacodylic Acid and Cacodylates (<i>continued</i>).		Canadian Hemp. See Apocynum.	
Physiological Action	719	Cancer	752
Untoward Effects and Poisoning	721	General Considerations	752
Therapeutic Uses	721	Frequency of Cancer	752
Cactus Grandiflorus	725	Etiology	755
Physiological Action	726	Geographical Distribution	759
Therapeutic Uses	726	Distribution in the Body	762
Cade, Oil of	726	Influence of Age	764
Mode of Employment	727	Hereditary Influences	765
Therapeutic Uses	727	Exciting Cause	766
Caffeine. See Coffee.		Influence of Occupation	770
Caisson Disease. See Compressed Air; Disorders Due to.		The Essential Nature of Cancer	771
Cajuput Oil	727	Pathology	775
Mode of Employment	727	Malignant Tumors of Mesoblastic Origin	777
Therapeutic Uses	727	Malignant Tumors of Epiblastic Origin	781
Calabar Bean. See Physostigma.		Mixed Malignant Tumors	782
Calcium	728	Chemistry of Cancer	786
Preparations and Doses	728	Symptomatology	786
Physiological Action	731	Diagnosis	791
Calcium Poisoning	733	Acid Oxyprotein Test	792
Therapeutics	733	The Blood	792
Sodium Lactate	733	Antitryptic Index	793
Calcium Chloride	736	Complement Deviator Power	793
Calcium Hypophosphite	738	Cytolytic Power	794
Calcium Hydroxide Solution (Lime Water)	738	Meiostagmine Reaction	795
Calcium Carbonate	738	Reaction in Vivo	795
Prepared Chalk or Chalk Mixture	738	Abderhalden Test	796
Local Uses	738	Treatment	796
Calomel. See Mercury.		1. Surgical Treatment	798
Calumba	739	11. Non-surgical Treatment	800
Preparations and Dose	739	1. Diet and Hygiene	800
Therapeutic Uses	740	2. Drugs and Chemical Agents	801
Calx. See Calcium.		Chemical Agents	802
Cammidge's Reaction. See Pancreas, Diseases of.		Organotherapy	803
Camn Fever. See Typhus.		Local Destructives	805
Camphor	740	Medical Applications	808
Preparations and Dose	740	X-ray	809
Physiological Action	741	Radium	811
Poisoning	743	Finsen Light	813
Treatment of Camphor Poisoning	747	Leucodescent Lamp	813
Therapeutics	747	Fulguration Treatment	813
		Sera and Vaccines	815

SAJOUS'S ANALYTIC CYCLOPEDIA of PRACTICAL MEDICINE

A

ANOREXIA NERVOSA.—**DEFINITION.**—The word anorexia, which is derived from a Greek word *ἀρεξίς* and *a* privative means literally “without longing.” It has been used to signify deficiency or loss of appetite for food.

GENERAL CONSIDERATIONS.—The symptom is one which, as is well known, is met with in a variety of conditions, such as disease of the digestive tract, organic and functional, in febrile states, in states of great exhaustion, in the cachexia of malignant disease, in various insanities, in psychasthenia, and in hysteria. The term anorexia nervosa was first employed by Sir William Gull in a paper before the Clinical Society in 1874. According to Gull, the affection manifested itself at times by a disgust for animal food especially and at times in its more pronounced forms in a disgust for all foods. The patient is irritable, obstinate, and restless, sleep is much disturbed, and the affection is at times so pronounced as to threaten life unless medical measures intervene. Gull considered the affection as a nervous one in which especially the vagus is involved. Gull's observations were

soon confirmed and extended by Lasègue, Charcot, Huchard, Sollier, and others, and the term anorexia nervosa has come to signify in reality the loss of appetite met with in hysteria; in other words, it is synonymous with anorexia hysterica.

Anorexia nervosa is, as a rule, readily differentiated from the loss of appetite met with in organic disease of the stomach, catarrh, atony, and allied disorders, and from the anorexia met with in cachectic, diathetic, and exhausted states. Its differentiation from the anorexia met with in other nervous affections, while in reality equally clear, demands a moment's consideration. The one nervous affection in which loss of appetite is a common and pronounced symptom and often rises to the degree of absolute refusal of food is melancholia. In melancholia, anorexia is so common a symptom as to be almost as characteristic as the depressive mental state itself. So common is it that it has come to be known by a special term, *sitiophobia*, and the symptom ranks in importance almost with the delusion of the unpardonable sin. It is to be distinguished from anorexia nervosa by the differentiation between

hysteria and melancholia. It is invariably associated with the state of painful emotional depression, begins when this begins, becomes more pronounced as this becomes more pronounced, and lessens as this lessens and fades away. Even in melancholia without delusions and without hallucinations, melancholia *sine delirio*, this one feature will serve to differentiate the anorexia from anorexia nervosa. It is only in subacute and lucid melancholia, hypomelancholia, that a difficulty might arise. Here again, however, the anorexia, in keeping with the lessened degree of mental depression, is itself less pronounced; though it must not be forgotten that even patients with hypomelancholia may attempt suicide by starvation. It must be remembered that the mere absence of hysterical stigmata will not serve to differentiate such a case, as anorexia nervosa may be the only outward or tangible manifestation of hysteria. The hysterical mental attitude is however always present;—the abnormal suggestibility and emotional mobility.

As regards neurasthenia, the question of anorexia practically never arises, for in the neurasthenic, despite the digestive disturbances, the appetite is uniformly or almost uniformly exaggerated; never lost. The same is true of psychasthenia; here the appetite is also usually exaggerated, and indeed in some instances amounts to a bulimia. However, in a limited number of cases, because of the atonic indigestion usually present (associated as this is with slowness of digestion, distention, belching, and perhaps regurgitation) the patient may develop a refusal of food, *i.e.*, an obsession with regard to food, or he

may develop a special fear in regard to eating. Indeed, Buvat has pointed out that anorexia occurring in a psychasthenic is the expression of a phobia. As already stated, it is quite rare.

SYMPTOMS.—A consideration of anorexia nervosa necessitates a consideration, however brief, of the nature of hysteria, of which anorexia nervosa is but a symptom. Hysteria may be briefly defined as a nervous affection the various symptoms of which bear the impress of a psychic origin. How thoroughly this conception of hysteria has taken hold of the modern medical mind is evidenced by the views advanced in the last few years by Babinski. Babinski holds that hysteria has its origin entirely in suggestion, and that its symptoms are curable by persuasion, and he has proposed as a new name for the affection the term *pithiatism*, which literally means curable by persuasion. However, whether we accept the radical interpretation of Babinski or not, the fact of the psychic origin of the symptoms must ever be borne in mind. These symptoms embrace the range of those possible under the circumstances, and, therefore, include not only mental, motor, and sensory symptoms, but also visceral symptoms (see article on Hysteria). That in hysteria, therefore, we should meet with involvement of the digestive tract is not surprising. It is perfectly conceivable that, just as an arm may be hysterically paralyzed, *i.e.*, elided from the field of conscious activity as regards its motion and sensation, so may the organic sensation of hunger, the desire for food, be elided, cut out of the consciousness of the patient. Again, it is conceivable that, just as

hysterical pain may occur in the head, the trunk, or a limb, so may it occur in a viscus and that viscus the stomach. Further, it is extremely probable that the mucous membrane of the stomach is every now and then the seat of areas of painful hyperesthesia identical in nature with the painful stigmata found upon the skin, such as the inframammary and inguinal tenderness. We know definitely that such areas are found on all the mucous membranes accessible to our observation, namely, the conjunctiva, the mucous membrane of the mouth, the nose, the pharynx, the vagina, the rectum. That they equally make their appearance in less accessible structures, such as the stomach and bladder, there is in my mind no doubt.

Anorexia nervosa is usually present in association with other and unmistakable signs of hysteria. However, if the anorexia nervosa be very pronounced, the other signs become less prominent and may even fade away. Indeed, as already stated, anorexia nervosa is now and then the only objective or tangible symptom present except, of course, the one cardinal symptom, the attitude of mind.

As a rule, anorexia nervosa develops gradually and its early signs may be insignificant and attract but little attention. Thus, it may make its appearance in a case of hysteria in which other well-marked hysterical manifestations are already developed. In such instance it may merely complicate the existing condition, and quite commonly anorexia making its appearance under such circumstances is not very pronounced and may even prove transitory. However, when it makes its appearance as an inde-

pendent or as the first well-marked symptom of hysteria, it may prove very persistent and obstinate. Equally true is this of cases in which anorexia makes its appearance in the midst of other well-established symptoms, but gradually substitutes these symptoms so that after a while it alone remains, —either alone or as the most prominent symptom.

The first objective symptom of anorexia nervosa is a diminution of the appetite. This diminution becomes gradually more and more pronounced until finally a complete refusal or disgust for food is developed. If in response to the urging of physician and friends food is taken, it is taken with apparent effort, often with exaggerated attempts at swallowing, usually with spitting up of the food, actual regurgitation, and finally vomiting. This vomiting, as is well known, may be very obstinate and may follow every attempt to administer food. Curiously enough, though this is the exception, a patient under these circumstances may declare herself to be hungry,—hungry and yet unable to eat. In the average case, however, all instinctive feeling for food seems to disappear; hunger and thirst are equally absent. Strangely, too, food, even when retained, may not give rise to the normal sensation of satiety.

At times the disgust for food is so pronounced that the patient cannot bear even to think of taking food; the mere suggestion of food is followed by manifestations of disgust and nausea. It would seem also that during the height of an attack of anorexia nervosa the patient is often unable to recognize the food properly. There is quite commonly complaint

that the food tastes bad or that it is disgusting: the eggs are not fresh, the milk has turned, the meat is tainted, there is something in the broth, the water tastes of gas, etc.

While cases of anorexia bear a general resemblance to each other, marked differences may obtain, both as to the mode of origin and as to the severity or the details of the symptoms. Thus in one group of cases, as has been already indicated, there is primarily a disturbance of the organic sensations of hunger and thirst or an actual elision of these sensations. There is in these cases not the fundamental disgust for food so commonly met with in the other forms. Not infrequently too, such a patient, having been induced to eat, feels the appetite returning. In other words, the normal desire for food returns when the mere mechanism of the taking of food and digestion is set in motion. Such cases are comparable to the disappearance of an hysterical retention of urine by the suggestion furnished by running water, or the disappearance of an hysterical palsy by the institution of passive movements. As would seem probable on *a priori* grounds such cases yield, as a rule, quite readily to treatment and are rarely persistent unless complicated by untoward and inadvertent suggestions.

More commonly, however, cases of anorexia nervosa are not so simple. In by far the larger number of cases the origin is somewhat as follows: The patient complains usually for a time that food gives rise to pressure, to pain, to distention, to gas usually in great quantities, and upon this basis develops a loss of appetite, fear and disgust of food. Pain may be referred to various regions of the

stomach, and this pain may be associated with tenderness, an hysterical hyperalgesia. This tenderness is most frequently marked in the pit of the stomach. It apparently is in the stomach, probably in its mucous membrane, and as already indicated is analogous to the painful areas found upon the cutaneous surfaces. Physicians sometimes describe cases presenting these symptoms as gastralgia, failing to recognize their hysterical character. Further, the epigastric tenderness, it should be borne in mind, must not be confounded with the pain met with in gastric ulcer. However, gastric ulcer may be simulated, especially if there be present spitting of blood, a symptom that some hysterical patients appear to be very expert in producing. It is hardly necessary to point out here the necessity, in given cases, for an analysis of the gastric contents, microscopical and chemical, in making the differential diagnosis.

The most difficult cases of anorexia nervosa are those in which pain makes its appearance immediately after the introduction of food, or in which hysterical distention immediately ensues. The latter symptom is sometimes pronounced to an incredible degree. At times, a small quantity of milk or even a swallow of water is followed by a violent and excessive distention of the stomach and, in a case recently under my observation, by an enormous ballooning of the entire abdomen, rapid pulse, and difficult breathing. In other cases, the patient does not complain of pain and does not manifest distention, but the taking of food results in restlessness, fear, palpitation, sweating, faintness, or in the onset of hysterical crises

which have gagging, retching, regurgitation, or vomiting as their central features.

As a rule, by the time that these patients reach the physician's care, they have narrowed their diet to an extreme degree. Frequently it has become limited to a small amount of liquid food, or, as in another patient recently studied by me, to a few teaspoonfuls of ice-cream daily. That great loss of weight and even marked emaciation may ensue under such circumstances goes without saying.

There is a third group of cases, in which the anorexia nervosa has still another mode of origin. Here the anorexia is the outgrowth of unhealthy ideas, unphysiological notions on the part of the patient. Very many women entertain the idea that they must not become stout, that they must preserve their shape, that it is vulgar to be fat, and that it is gross to eat much. Given these ideas and the hysterical neurosis, extreme and difficult anorexia nervosa may result. Many a patient already absurdly thin views with the utmost alarm the slightest possible addition to her weight and obstinately resists the administration of food, if only in physiological quantities. In other cases, a smaller number, the patient has acquired the absurd notion that the free taking of food is not healthy, and that body and mind are both best off when the food is very limited in amount. Usually vanity of figure is again the real explanation. The patients of this group are usually extremely difficult. They are invariably far below weight. By the time they come under medical care, their diet has become very restricted. They have usually adopted some special

form of diet, or have developed obsessive ideas in regard to the most ordinary and most wholesome foods. Milk is almost always under ban, and this is usually true of eggs. Sometimes meats are included or it is vegetables which are tabooed; sometimes it is everything or almost everything.

The course of anorexia nervosa when once established, no matter what its mode of evolution, is largely as follows: The patient becomes more and more confirmed in her attitude as regards food. Emaciation becomes more and more pronounced, and her bodily and mental activities become more and more limited. In bad cases they become confirmed bed-ridden invalids who employ their feeble remaining energy to resist the taking of food, and who fight doctor and nurse silently, tenaciously, and at times effectually, for death may actually supervene. Thus, Osler describes a fatal case, the patient weighing at the time of death only 49 pounds. The autopsy disclosed nothing. They may get to the stage of refusing to take food altogether voluntarily, and if the attempt be made to feed them with a spoon avert their faces, compress their lips, bury their heads in the pillows. Sometimes hysterical struggling, weeping, collapse may ensue. Other patients will complain that they are too weak to masticate their food, that swallowing tires them, that it makes the blood rush to the head, makes them dizzy, makes them faint. Solid food is first discontinued, and then the liquid foods are gradually restricted until they become grossly insufficient in amount.

The full development of a typical

anorexia nervosa is usually a matter of some time, usually weeks, often months, and occasionally years. The symptom, however, as already stated, may make its appearance spontaneously and rapidly, just as do other hysterical manifestations. Charcot described the case of a girl of 18 who, having witnessed the killing of a child by a railroad train, became sad and depressed, was troubled by distressing dreams. About two months later she lost her desire for food. This loss appeared suddenly and supervened upon an attack of suffocation (*globus hystericus*) while she was in the act of taking food. Upon subsequent attempts to take food, the *globus* promptly reappeared.

It is important to call to mind a few other features. First, while in many cases of anorexia nervosa there is undoubted loss of weight and even emaciation, prolonged refusal of food may coexist with remarkably little loss of weight and strength. In many of these cases, food, of course, is taken and probably in larger amounts than is admitted by the patient. In others the fact that the patient is in a condition of absolute quiet in bed diminishes the actual need for food. In some cases again, fraud can justly be suspected. It is further noteworthy that in cases in which there is but little loss of weight and strength there is usually no vomiting. Secondly, as regards the vomiting, this can hardly be regarded as a genuine automatic ejection of food by the stomach. Nausea, genuine nausea, while it may be claimed, is often absent, and the act by which food is ejected is more like a regurgitation than a genuine vomiting. Sometimes the food is ejected before

it reaches the stomach, a condition which has given rise to the term *esophagismus*. At other times the act of swallowing is evidently imperfectly or spuriously performed. Although the patient seems to make exaggerated efforts, she fails to swallow and declares that the food will not go down. At other times she frankly makes no attempt to swallow the milk or other liquid introduced into the mouth, but allows it to dribble out or frankly ejects it.

Finally, owing to the insufficient ingestion of liquids, the skin may be harsh and dry and the urine greatly diminished in amount and much concentrated.

Nebelthau observed a case of hysterical anorexia in which, while there was no evidence of visceral disease and no sugar in the urine, the breath smelled of acetone, the urine giving a most marked reaction of acetoacetic acid. There was vomiting, and the vomit also contained acetone. With sufficient nutrition the smell of acetone in the breath, the reaction with ferric chloride in the urine, and the increased ammonia excretion disappeared.

The cases of hysteria which present anorexia nervosa, let it be repeated, are almost always young women. While I have met with this symptom in women of middle life, I have never seen it assume a grave form at this age. A similar statement may be made with regard to male patients. While diminution of appetite may be noted among male cases of hysteria, I have personally never seen a case of sufficient gravity to be characterized as an anorexia nervosa. The patient is most frequently a young woman; sometimes a mere child. Two of the worst cases I have ever seen, however, have occurred in women between 30 and 40.

Neisser and Brauning have often observed patients who grew thin because their appetite was appeased with a few mouthfuls of food and they did not care to eat more and consequently were starving although their appetites were good. A research showed that it depended on the pressure within the stomach from the food itself or from the peristaltic contraction of the stomach or from pressure from without as from a tight corset. Beside laying aside the corset, suggestion served to train the young girls to eat normally and enjoy the entire meal with appetite instead of being satisfied with a few mouthfuls, but this once accomplished they rapidly took on weight. In another group of patients early satiation was traced to excessive tonicity of the stomach walls and hasty eating.

TREATMENT.—The treatment of anorexia is of course primarily that of the underlying hysteria, and in order that this shall be successfully combated it is of the utmost value, whenever practical, to institute a radical course of rest treatment with complete isolation. Whether we accept or reject the somewhat revolutionary views of Babinski, we must admit that Babinski has rendered invaluable service to our understanding of hysteria by accentuating the fact that in hysteria suggestion plays an enormous rôle. The indications are to place the patient in whom such profound perversion of function as anorexia nervosa has occurred amid surroundings and under conditions in which it will be possible to bring about a restoration to simple physiological living and at the same time to protect the patient against the evil influences of harmful suggestions such as they are almost always subjected to by their well-meaning, but mistaken relatives and friends. It is quite clear that a **rest treatment** in bed with complete isolation offers the most favorable conditions for the

carrying out of such a plan. For the details of the rest treatment as applied to hysteria in general, the reader is referred to the section which treats with this affection especially. Suffice it to say here that the rest in bed should be absolute and continuous for a time; usually a number of weeks are required. Secondly, simple **bathing** such as will not shock or disturb the patient, bathing with lukewarm or slightly warmer water, carried out between blankets in bed, followed or not, according to circumstances, by a gentle **alcohol rub**. Usually, gentle **massage**, not too vigorous and not too deep, carried out in the latter part of the day, preferably in the evening, before the hour for sleep, proves of great value. In giving the massage, if there be an anorexia nervosa, it is important that the nurse should omit rubbing the epigastrium or the abdomen generally; at least at first because of the painful tenderness so frequently present in the epigastric region. Later on, of course, during convalescence, the massage may include the region of the stomach as well as the abdomen generally. Care should also be exercised by the nurse that in giving the massage she makes no untoward suggestion or comment as to reasons for rubbing certain portions of the trunk and not others. It is unnecessary to add that the nurse should be one who is especially trained in the management of nervous cases.

The views of Babinski are especially to be borne in mind as to the curability of hysterical symptoms by persuasion, a fact, of course, long known, but upon which he has with great justice laid renewed stress. **Persuasion** in all its forms must be

employed, and the suggestion of getting well, both directly and indirectly, must constantly pervade the sick-room.

The cachexia of cancer is due in large part to the loss of appetite. In this as in other conditions with anorexia, much can be done by fostering the appetite. It is second only to removal of the cause. The main point is to prepare the food so that its taste will be attractive to the patient. Sternberg (*Therap. der Gegenwart*, Mar., 1913).

The treatment of the special symptoms of anorexia is one which usually offers many difficulties. No general rule as to the food which should be administered can be given. In many cases much can often be accomplished by making an agreement with the patient as to the kind or kinds of food which shall be first attempted. As a rule, the patient at first rejects every proposition that is made by the physician, but after a little gentle argument and persuasion some basis of agreement can be reached. If possible this should include milk, and, indeed, if it be limited to milk the physician has no great cause for complaint. The patient may insist upon an absurdly small quantity being given at a time. If so, the compromise reached should be adhered to, bearing in mind that much can be gained by frequency of feeding. If milk be rejected, white of egg or albumin water may be attempted, though this must be regarded as merely a temporary expedient. As a rule, the patient becomes accustomed to the food as being given, she feels that no advantage is being taken of her, acquires confidence in both the physician and the nurse, and can be persuaded in the course of a few days to allow the milk

or other liquid food that is being given to be increased. Whether the milk had best be modified in some way, peptonized, skimmed, diluted, made alkaline by the addition of lime water, salted or otherwise flavored, must depend entirely upon the resourcefulness and the tactful judgment of the physician. Suffice it to say that most is gained if whole milk be administered. It may be wise to skim this slightly, so as to diminish the amount of cream which is taken. Sometimes, it is found that if the milk is diluted with some carbonated water, such as Vichy, fountain soda, Apollinaris, and the like, it is well tolerated. Occasionally, cases are met with in which liquids, as well as solids, are equally rejected. In such instance we have to resort to some of the following expedients; for instance, the yolk of an egg which has been very thoroughly boiled may be powdered and mixed with sufficient salt to make it quite salty. Small quantities of this can be placed upon the tongue and the patient encouraged to swallow it. If only a beginning can be made in the way of stimulating the retention of food by the stomach, all is gained, for the patient will soon find that other foods can be retained. At times, a very small quantity of finely minced ham—a mere fragment given by a teaspoon at intervals—will be retained. At other times a small piece of dried beef can be chewed by the patient and the juice swallowed. Later, such a patient can be persuaded to chew a small piece of steak and to swallow the juice. The primal effort and object of all the attempts at feeding should be the restoration of the belief on the part of the patient in her abil-

ity to retain food, and, after all, the various means by which this can be accomplished depend upon the case and must of necessity be very varied. On the whole, medicines had best be avoided, as the patient is apt to reject these as promptly as the food. However, it is not infrequently found that **bromides** are retained when other medicines are not tolerated. If so, much is gained. Twenty grains (1.3 Gm.) of the **bromide of ammonium**, with a little **aromatic spirit of ammonia** dissolved in peppermint water and well diluted, are frequently retained and, as it were, gratefully appreciated. Sometimes this is not the case. Under such circumstances, we now and then find that **morphine** in small quantities is well borne. It should be given in doses of $\frac{1}{32}$ grain (0.002 Gm.), repeated at intervals of one-half hour to an hour until a gentle sedative impression has been made. Usually this occurs by the time an eighth has been given. Larger doses of morphine may be employed, but their liability to induce nausea of themselves must be borne in mind. As a rule, cases of anorexia bear small doses well. The morphine may be retained if dissolved in a small quantity of water. Sometimes it is best administered in a few drops of **brandy** or in a teaspoonful of iced **champagne**. Gradually the nervousness and anxiety of the patient are allayed, and the retching and vomiting are brought under control. Small quantities of milk can now be given, and, little by little, the patient's confidence in her ability to take food becomes restored.

As already stated, we now and then meet with a deep epigastric tenderness which from the absence of other

signs suggests that the mucous membrane of the stomach is itself the area of a painful hyperesthesia, a true sensory stigma. Small doses of **cocaine** are sometimes beneficial in such cases. It should be administered in a manner similar to the morphine or may indeed be combined with the latter. **Champagne** by itself has not proved in the writer's hands a very successful expedient for the relief of anorexia nervosa. There is no objection, however, to its trial in cases in which all foods fail. **Carbonated water** alone sometimes proves of value.

The patient's confidence in her ability to take food having been somewhat restored, we should be content with giving small quantities, a teaspoonful or a tablespoonful of some liquid food every hour or two being sufficient. A start having been made, the amount can be increased little by little until, after days and it may be weeks, a full feeding is reached. The approach to solid food should, of course, be cautiously made. That it should be soft or semisolid and small in quantity goes without saying. Special effort to please the fancy and the palate may be made, such, for instance, as a very small and very thin sandwich of toast containing between its layers a small quantity of scraped beef, the latter being well salted and flavored, perhaps, in addition with a minute dash of pepper. A sandwich made similarly with a small quantity of the yolk of a hard-boiled egg may also be tried. Minced ham and a small piece of bacon are among the other articles which naturally suggest themselves.

It every now and then occurs that for several days at a time nothing

whatever is retained, and under these circumstances it is proper to resort to **feeding with the nasal or stomach tube**. Especially is this advisable in cases in which the trouble appears to be especially due to difficulty of swallowing, or esophagismus. Quite frequently it is not necessary to resort to this expedient more than once, the mere preparation for the procedure being often sufficient to stimulate the patient to take a small quantity of food naturally. Now and then, tubal feeding in bad cases of anorexia nervosa is unsuccessful because the patient rejects both the tube and milk as fast as they are introduced. In such instances it is perfectly proper to give, twenty minutes before the feeding is attempted, a hypodermic injection consisting of **morphine**, $\frac{1}{8}$ to $\frac{1}{4}$ grain (0.008 to 0.016 Gm.), and **scopolamine**, $\frac{1}{200}$ to $\frac{1}{100}$ grain (0.0003 to 0.0006 Gm.). As a rule, the sedation and quiet produced by the hypodermic greatly facilitate the giving of tubal feeding, and, a large quantity of food having been given and retained, the victory may have been gained, the patient having become convinced of her ability to retain the food.

Debove insists on the necessity of compelling the patient to eat, by no matter what method. The appetite will return on eating. That a certain amount of **compulsion** is necessary is attested by a case of Drummond's, that of a neurotic young man of 25 years, weighing 70 pounds, who had been lying in bed for five years, and who gained 14 pounds after a month's treatment. Baruch advises **hydrotherapy and lavage of the stomach**.

Hypodermic medication should, of course, be avoided except in exceptional instances. The relief given is very prompt and gratifying, but, as the relief is temporary only, the patient

may soon insist upon a repetition of the dose. Occasionally when bromide and morphine are not tolerated by the stomach, **suppositories of opium** may be administered. These, for obvious reasons, should be used for a short period of time only.

Finally, we may add that it is rarely necessary to resort to **rectal feeding** in anorexia nervosa. If tried, it should be persisted in for a short time only, as the moral effect of the procedure is bad, the patient being confirmed in her opinion that there is something serious the matter with her stomach.

In the average case of anorexia nervosa, the difficulty of administering food is not so profound as would perhaps be implied by the foregoing paragraphs. Most frequently the patient objects strenuously to some special article or articles of diet; strangely enough they are frequently the very articles that the physician most desires to give.

J. P. Crozer Griffith observed a case in a male child in which there was a strong disinclination to try any food which was new to him. He refused to taste ice-water until after his sixth birthday, and then expressed surprise that it was so good. With regard to all new articles of diet, his reasoning was voiced in his remark that "he would not taste it because he had never eaten it before." This expression on the part of the child is clearly the keynote of the whole situation, according to Griffith. Instead of disappearing soon, as is usually the case in convalescent infants, this dislike became intensified, and extended, finally, to all food and methods of giving it, except the two to which the child had already become accustomed, viz., milk sucked from the breast and bread eaten from his own hand. The anorexia was now as marked and clearly as hysterical in nature as that seen in patients of a greater age. Only the **forced feeding**

prevented the excessive emaciation which often occurs in older patients.

Case of an 11-year-old girl who absolutely refused to eat. On admission to the hospital she weighed 16 kg. She was exceedingly nervous and showed several stigmata of hysteria. There were several zones of anesthesia over the lower extremities and the pharyngeal reflex was absent. There was obstinate constipation. This patient made a complete recovery and in six weeks gained 10 kg. The treatment consisted solely in **rest in bed** and **persuasion**. No drugs of any kind were administered. The child was kept in the large general ward without isolation. The influence of the visits of the child's family was bad. After such visits she would have attacks of vomiting and refuse all food. Finally the parents were forbidden to see the child.

Removal from the home and all family influences must be insisted upon. Absolute repose in bed with or without **hydrotherapy** and tactful persuasion to partake of food are deemed the most satisfactory measures. Comby (Archives des méd. des enfants, Dec., 1909).

Case of anorexia nervosa in a child about 1 year old, apparently in normal health. When given a new nipple it refused to take food afterward. Every possible method and kind of food was employed to persuade the child to eat, but without success. At length **gavage** was instituted and carried out for several days; after this the child again began to take food in the usual way. N. G. Orchard (N. Y. State Jour. of Med., Jan., 1914).

This difficulty may be met in a number of ways. When possible the endeavor should be made to bring about in the patient an **autosuggestion** favoring the dietary it is desirable to prescribe. This, of course, must be accomplished by indirect methods. Thus the article of food,

most often it is milk, may be emphatically and ostentatiously forbidden, or the nurse, having been previously instructed, should in the patient's presence mention the matter of milk. The physician in reply should treat this matter as of no consequence or possibly ignore its mention by a shrug of the shoulders. Not infrequently the patient, finding that milk is not being forced upon her or not even mentioned in her presence, asks the physician whether he never in such cases as hers prescribes milk and whether a trial of the milk in her case might not prove beneficial. Especially is this likely to come to pass if the amount of other food has been so limited as to be grossly insufficient. However, the indirect method of suggestion or the suggestion of the opposite not infrequently fails, and here tactful persuasion, the striking of a hard and fast agreement, as already mentioned above, should be attempted. Almost always it can be secured. The advantage gained is exceedingly great, and if followed up in the proper manner it will prove of enormous usefulness in bringing about a successful issue. Very much, of course, must be left to the tact of the physician and his intimate knowledge of the mental make-up of the patient. The essentially psychic character of the symptoms should never be lost sight of.

F. X. DERCUM,
Philadelphia.

ANTHRAX.—DEFINITION.—

A malignant pustule due to infection by the *Bacillus anthracis*, through which, from an infected center, it may spread over the body or attack the intestinal tract, resulting in a general infection.

It is also known as "wool-sorters' disease" in man and "splenic fever" in animals.

It is due to specific bacilli which may attack every species of domestic mammal, and for this reason may become one of the greatest scourges of animal life. Man is by no means immune, although, fortunately, the malady as it appears in the human subject is usually less acute than the form seen in cattle and sheep.

When the lesion occurs in dense, highly vascular superficial tissues of man, it is often termed *anthrax carbuncle* or *malignant pustule*; when it occurs in loose tissues *anthrax edema* is witnessed. *Internal anthrax* refers to lesions of the internal organs.

SYMPTOMS.—Before the bacteriology of the disease was known, its diagnosis was not always easy. The most frequent primary lesion is in the face. The first symptom is a sense of itching, followed by a red spot resembling a flea-bite; a small vesicle forms soon afterward, containing a bluish fluid. The surrounding skin is somewhat indurated and swelled. This changes into a black spot, which soon becomes gangrenous. If the edema continues, fresh crops of vesicles often appear, undergoing the same change, and infecting the adjacent lymphatic glands. The period of incubation is from one to three days, while the development of the local symptoms occupies from three to nine days. A line of demarcation may then form, and the slough separates. No pus is present. General disturbance begins only a day or two after the manifestation of the disease. There may be no fever, but in some cases, especially when the face is involved, a sudden rise of temperature may present itself,

denoting a dangerous condition. When located in the eye-lids considerable cicatricial deformity may result.

Fifteen cases came under the personal observation of the writers, in the Philadelphia Municipal Hospital. All had been victims of their peculiar vocations. Six worked regularly in hair; 5 were steadily handling hides; 2, cases 4 and 10, hauled hides incidentally; 1 worked in leather, and 1 skinned a cow dead of what was supposed to be anthrax. The diagnosis was confirmed bacteriologically after coming under observation in all except cases 3 and 12. In each of these the anthrax bacillus was found in the Pennsylvania Hospital before admission. In 6 patients the pustule was on some part of the face, in 5 on the neck, in 2 on the forearm, and in 1 on the finger. Fourteen were males. B. F. Royer and E. Burvill-Holmes (Penna. Med. Jour., Sept., 1908).

Unique case of anthrax septicemia, the result of a bullet wound. Marked contrast was soon noted between the apparently insignificant wounds of entrance and exit and the coexisting intense general prostration, the wounds even on the fifth day showing but little tendency to suppuration. The diagnosis was made by blood-culture, injection into a guinea-pig, and subsequent rapidly fatal course of the disorder. Couteaud (Bull. de l'Acad. de Méd., Dec. 8, 1914).

In 5 cases observed by the writer, the infection had followed comparatively slight wounds with crushing of muscle tissue. The path of the projectile was a tract of putrid mortification and edema developed early. It spread to the end of the limb but not up to the trunk. Death occurred from heart failure in every case, although the conditions did not seem at all menacing. Scalone (Policlinico, Nov., Surg. Sect., 1917).

Headache, nausea, and pain in the muscles appear, with a weak and rapid heart. There is slight icterus. The prostration is great, and the last

stages of the disease finds the patient almost in the algid stage of Asiatic cholera.

When infection takes place through the alimentary canal, the disease begins with debility, depression of spirits, malaise, and probably a chill. In addition, the symptoms point to the intestines. Hemorrhages occur from the mouth and nose; vomiting is followed by a bloody diarrhea. The diagnosis is, however, extremely difficult, and the microscopic examination of the blood or an inoculation of an animal furnishes the only conclusive evidence.

Ascoli Reaction.—The resistance to heat of certain precipitins, especially those of anthrax in cattle and swine plague, is considered important by A. Ascoli (Policlinico, Feb. 4, 1912). The reaction is obtained in a few minutes by simply boiling a little of the material in 3 or 5 times the amount of physiologic salt solution and pouring the cooled filtrate on the precipitating serum. The ring and zone at the point of junction are characteristic for these two diseases in domestic animals, while with extracts from pellagra, septicemia and lymphadenitis the reaction is invariably negative. The **Ascoli reaction** was found to be specific by Izabolinsky and Patzevitch (Roussky Vrach, May 5, 1912). The reaction occurs with fluids and tissues which have undergone putrefaction (for forty days, in the author's experiments), and is most marked when a solution from the spleen is employed.

Case in which an anthracemia was present and was followed by recovery. The disease had exhibited the characteristic 4 stages of cutaneous anthrax characterized by a persistent increase in symptoms, and the presence of *B. anthracis* in the circulating blood. Graham and Detweiler (Jour. Amer. Med. Assoc., Mar. 9, 1918).

ETIOLOGY.—Anthrax was one of the first diseases traced to a specific micro-organism.

Pollender discovered in 1849 small rod-shaped bodies in the blood of animals suffering from anthrax, but Davaine, in 1863, proved their etiological significance. Pasteur and Koch, observing that the bacilli bore spores, cultivated them successfully outside of the body, and then produced the disease by inoculating animals with the pure cultures.

The anthrax bacilli are large rods, with a rectangular form, caused by the very slight rounding of the corners. They measure 5 to 20 microns in length and are 1 to 1.25 microns in breadth. They form long threads, in which the single bacterium can be made out. At times isolated rods occur. In this stage granular bodies appear in the protoplasm of the bacilli. They eventually form glistening oval spores, one of which lies in each segment of the long thread, giving the threads an appearance of a string of beads. The bacilli soon break up, and the spores become free. In this condition the spores become highly resisting and can be preserved a very long time. If again placed under favorable circumstances, each spore will germinate into a mature cell. Spore formation takes place only at temperatures ranging from 18° to 43° C., 37.5° C. being the most favorable temperature.

The anthrax bacilli can rapidly be stained by aqueous solutions of aniline dyes, and also by Gram's method. The spores are best stained at a high temperature by means of Ehrlich's aniline-water-fuchsin solution or Ziehl's solution containing carbolic acid, instead of Ehrlich's fuchsin solution.

The virulence of anthrax bacilli can be attenuated in various ways, such

as subjecting them to a high or low temperature or making the culture grow for a long time—twenty-four days or so—at a temperature of 42° or 43° C. By treating them in some such manner it is possible to render anthrax bacilli entirely innocuous (Koch, Loeffler). Pasteur rendered sheep and cattle immune against anthrax by inoculating them with a culture which grew at a temperature of 42° C.

Dogs, pigs, and the majority of birds are immune from anthrax; also rats and frogs under ordinary conditions. But if a frog in whose lymph-sac are placed anthrax bacilli is put in an incubating apparatus, he will quickly die of anthrax. Birch-Hirschfeld and others have proved that anthrax bacilli can be transmitted from mother to fetus *in utero*.

Experiments to determine the influence of the serum of immunized animals. A sheep was immunized until it could bear the injection of 7 agar-agar cultures with but slight elevation of temperature. A lamb was immunized likewise to the highest degree, and blood was taken from the carotid artery of both animals in order to obtain serum. With the serum of the sheep it was actually possible to save from death a rabbit in which an extremely virulent culture of anthrax was injected, either after or simultaneously with the serum. Evident therapeutic results were obtained with it in animals that had received the anthrax bacilli previous to the injection of serum.

The pathogenic germ is disseminated by the excretions of diseased animals, or by the fluids which escape from carcasses of animals killed by the disease.

Because of the remarkable tenacity with which certain plots of ground retained their infection, Pasteur in 1880 reached the conclusion that the carcasses of animals dying from anthrax, even though deeply buried, retained their many infectious organisms and supplied them with such an amount of nutriment that they continued to multiply for years, and in this way produced an immense underground supply of virulent anthrax organisms.

The writer found anthrax spores in the earth of a place which had been used 6 years before for burying diseased animals. The *burying ground* was wanted as a playground, and the investigation was undertaken to determine whether it was safe for such use. The writer recovered anthrax bacilli 6 times by animal injections and twice by direct planting. W. v. Gozenback (Zeitsch. f. Hyg. u. Infektionskrankh., lxxix, 336, 1915).

Herds are infected, as a rule, by the ingestion of spores with their food when the latter has been contaminated in the manner described, the spores germinating in the intestines. Cattle and sheep being the animals most frequently infected, the occurrence of disease principally in men who handle the hides or wool of these animals is clearly accounted for. In man, however, infection may occur by the inhalation of infected dust from the raw material they handle as wool sorters. Hence the term "wool sorters' disease." Infection may occur through abrasions of the skin; in Cyprus, it is known to be transmitted through the bites of an ant-like insect (*sphangi*, Williamson), which obtains the spores from the carcasses of infected animals. It has also been transmitted by bone-dust of such animals (Neave).

Where tanneries are located upon or near to streams there is great danger that anthrax will be brought to them upon hides and then be scattered over

the low lands lying downstream from the point where the tanning process is carried on. This state of affairs exists especially near to those tanneries which work upon goat or sheep pelts from foreign countries. Infection in the form of spores adheres to these hides so persistently that ordinary fumigation fails to destroy it, and repeated outbreaks of the disease occur wherever such skins are unpacked and manufactured into leather. In making mention of this danger Professor Law writes:—

"Since 1892 anthrax has prevailed along the banks of the Delaware River for a distance of forty miles in New Jersey and Delaware, destroying from 70 to 80 per cent. of the farm stock. The great morocco industry on this river draws infected hides from India, China, Russia, Africa, and South America, and the spores are carried and distributed by the hides." H. J. Washburn (U. S. Dept. of Agriculture, Bulletin 439, 1911).

Outbreak of 25 cases observed within 4 months. Of these, 23 occurred in persons handling hides. It was confined to workers in tanneries where dried "China" hides were used. All of the hides had reached America in the same cargo and had come from a district of China in which anthrax was known to be endemic. W. H. Brown and E. Simpson (Jour. Amer. Med. Assoc., Feb. 24, 1917).

Insect bites, such as those caused by mosquitoes and stable flies, and commonly used articles such as shaving brushes, sheep skin caps (Rogers) have been found to transmit the disease.

Case of a young woman who had edema of the face, following a tiny pustule like a *mosquito bite*. The edema spread to the chest. The fluid gave a pure culture of anthrax. There was no history of anthrax and no other traceable source of infection. The patient died in a few days. W. H. Park (Med. Rec., Dec. 4, 1915).

To test insect transmission of anthrax, the writer transferred *stable flies* to healthy guinea-pigs with only a

few seconds' interval after biting the infected host, and in the other instance an interval of 10 minutes elapsed between the feedings. A total of 20 flies were used in the first experiment, and 30 flies in the second trial. The exposed animals died in both cases during the evening of the third day. Typical pictures of anthrax infection were present at the necropsy. In addition a substantial gelatinous and hemorrhagic edema was observed in the subcutaneous region of the area upon which the flies were applied in biting. The spleens of both animals yielded characteristic square-ended rods, which showed typical picture when tested with McFadyean's differential stain. Pure cultures were obtained from the spleens of the dead animals. The growth on agar resembled that of the initial pure culture, and spores produced on a potato medium stained quite typically. The agar cultures when injected reproduced the disease with fatal results in guinea-pigs used in later experiments. Similar results were obtained in all essentials when *horse flies* were employed to transfer the disease from the sick to a healthy guinea-pig. M. B. Maitmain (Public Health Reports, Jan. 9, 1914).

The writer observed 3 cases of anthrax in which the infection was conveyed by means of *shaving brushes*. Two of the cases survived, whereas in the third the disease proved fatal. Both used and unused shaving brushes from the same source were found to be infected with anthrax bacilli. Elworthy (Lancet, Jan. 1, 1916).

In a fatal case smears of the blood from around the pustule showed many anthrax bacilli, some of which were abnormally swollen. The shaving brush of the deceased was found to contain anthrax spores. E. H. Snell (Lancet, Jan. 29, 1916).

PROGNOSIS.—The prognosis of anthrax in man, when infection takes place externally, depends mainly upon whether appropriate treatment is un-

dertaken early enough. Lengyel and Koranyi, by adopting suitable local treatment, lost only 13 out of 142 cases. Although patients with anthrax resulting from internal infection (intestinal, pulmonary) very rarely recover, the introduction of artificial immunity, active or passive, by the use of vaccines or sera has served to materially decrease the fatality of the disease.

In recent years the occurrence of anthrax in human beings has undergone a notable increase and it is now regarded by students of industrial conditions as an occupational disease of moment. The mortality varies within rather wide limits; for example, the malignant anthrax edema of the face and neck is invariably fatal, largely because of infiltration of the soft tissues around the larynx, pharynx, and esophagus. In the same way the wool-sorter's disease, which is an anthrax septicemia with intense pulmonary and cerebral symptoms, and anthrax of the intestinal tract, are likewise deadly. In malignant pustule of the face, however, the mortality is 5 times greater than that of an extremity, in which only about 5 per cent. of cases terminate fatally. D. Symmers (*Interstate Med. Jour.*, xxiv, 1003, 1917).

The presence of bacilli in the blood greatly aggravates the prognosis. It indicates moreover, that vaccines and sera may be depended upon as efficient therapeutic agents.

The specific anti-anthrax serum of Sclavo (see TREATMENT) is said to have reduced the mortality to a marked extent. More recently still, the government authorities in the Argentine have been using normal bovine serum intravenously in large doses, and it is said that the results are even more favorable than from the use of specific antiserum. D. Symmers (*Interstate Med. Jour.*, xxiv, 1003, 1917).

PROPHYLAXIS.—The fact that French skins, since Pasteurian inoculation has been employed in French flocks, have been found to rarely cause anthrax speaks in favor of that method. Disinfection, even by formal, is uncertain.

The writers found spores in more than 20 per cent. of samples of hides, wool, hair, and bones, and importations from the Malay States, and also in samples that had been disinfected by the methods now in vogue. This obviously indicates that these methods are still imperfect. Glynn and Lewis (*Jour. of Hygiene*, June, 1912).

The bodies of animals which have died of the disease should be destroyed by incineration, if possible, while diseased animals should be excluded from the field. Watchfulness in this connection is a profitable investment, as far as cattle and flocks are concerned, while reducing the danger of transmission to man. Vaccine, *i.e.*, Pasteurian inoculation, has practically stamped out the disease among French herds, formal vapor, previously used, having been found not to penetrate the wool sufficiently. Those who are exposed to infection should observe strict cleanliness, and breathe through a fine nasal screen, to prevent contamination through the respiratory tract.

All dressings should be burned and the discharges of the patient disinfected with strong corrosive sublimate solution. As soon as vacated, the room should undergo rigid disinfection, owing to the marked resistance of anthrax spores.

Sobernheim's method of immunization is somewhat different and consists in injecting the animal with a mixture of bacilli and anthrax serum. This method is supposed to give the

rapid immunization of the passive method, and at the same time the more lasting immunity obtained by vaccination. The serum has been mainly used in animals, but extremely good results have been obtained in man; the usual dose is 5 drams, and intravenous injection is advisable. Both Sclavo's serum and Sobernheim's method may be followed by rise in temperature and sweating, after which improvement takes place in twenty-four hours (Emery).

In general, however, it is mainly as a prophylactic agent in cattle that serum has been found of value with the exception perhaps of Sclavo's serum, (see p. 19).

TREATMENT.—In man the disease remains localized a longer time than in animals. When it is clearly circumscribed it is possible to remove it more thoroughly. Complete excision of the affected part, by means of the **Paquelin thermocautery**, and subsequent **cauterization with nitric acid** are to be practised. In recent years, however, the tendency has been toward more conservative measures, on the plea that general infection is favored by surgical procedures.

When excision fails, the writer injects 3 or 4 syringefuls of 8 per cent. **phenol** into the edematous zone, it may effect a cure. An **ice bag** should be applied, although some physicians have successfully used heat. He then administers **antianthrax serum**, furnished by the U. S. Bureau of Animal Industry, Washington, D. C. The first dose is 35 c.c. injected, intravenously, followed from 8 to 16 hours by a second dose given intramuscularly or intravenously. This dose is repeated if necessary. **Salines** are also given in full doses and **strychnine**, $\frac{1}{40}$ grain (0.002 Gm.) every 4 or 5 hours.

The patient should have plenty of fresh air and should be kept quiet. A tracheotomy tube should be kept handy in case the edema reaches the larynx. D. G. Dudley (Jour. Amer. Med. Assoc., Jan. 5, 1918).

Referring to cutaneous anthrax, or malignant pustule, the writer advocates the method of Dr. Joseph C. Regan, of the Kingston Avenue Hospital, Brooklyn, which meets effectively cases where the inflammatory infiltration of the tissues is so widespread as to make operation out of the question.

It is also applicable to any surface anthrax lesion.

The cutting and destructive operations being discarded, **antianthrax serum** is introduced directly into the lesion itself by means of several small injections around the periphery of the eschar.

From 7 to 10 c.c. of the serum are used locally once daily; at the same time 20 to 40 c.c. are introduced intramuscularly, or intravenously, if the bacillus is found in the blood. Practically all the cases have been treated by this method. The death rate in 1920 has been 10 per cent., only 2 of 20 patients so treated succumbing to the disease. J. R. Graham (N. Y. Med. Jour., Dec. 11, 1920).

Live steam at 50° to 52° C. (122° to 132° F.) has been used with success by Gucciardello in 50 cases, the steam being carried from a boiling kettle of water to the lesion by a spout 2 centimeters wide through a pasteboard cylinder. From 5 to 7 applications are made at intervals of 1½ hours apart. During intervals the parts are covered with gauze dipped in hot water. The treatment is soothing from the start.

According to Koch, **bichloride of mercury** is the most effective poison for the anthrax bacilli, being capable of killing them when used diluted as 1 part to 300,000 of water. Consequently, it is a good plan to use, in

and around the affected part, injections of 1 to 100 bichloride or 2 to 5 per cent. **carbolic acid**.

In 42 cases of anthrax affecting the cutaneous and cellular tissues, the writer thoroughly but gently washed the area with 1:2000 **mercuric chloride solution**, dried well, then swabbed it with 10 per cent. tincture of **iodine** and some **alkali** applied. This was repeated daily for several days until the slough had come away. It took about 2 or 3 weeks for an ulcer to heal, which it did with very little scar as compared with the tissues involved. The fatal cases seen were those in which the vesicles had been opened. J. Palmar, Jr. (Jour. Amer. Med. Assoc., Nov. 6, 1915).

It is important to let the vesicle alone. When the blood-vessels and lymphatics are opened, a worse infection in the tissues around the vesicle will ensue. J. P. Wales (Jour. Amer. Med. Assoc., Nov. 6, 1915).

Russian authors have met with success by the energetic use of **carbolic acid** locally and internally. This measure has recently been used with success in several countries. The method employed by Sassi consists simply in the injection of 5 drops of **carbolic acid** into 3 parts of the carbuncles, *i.e.*, 15 drops in all, at one dose. This dose may be repeated again during the same day.

Salvarsan and **neosalvarsan** have been tried with apparently favorable results.

Case of anthrax treated with **salvarsan** intravenously, the dose employed being 0.6 Gm. (10 grains). The improvement was almost immediate. The temperature fell very rapidly to normal and the pulse became slower and fuller. The edema of the forehead and cheek, as well as the swelling of the neighboring glands, disappeared rather rapidly under treatment with warm applications of **Burow's solution**. Tincture

of **iodine** was used on the pustule. The scab separated after about a month and left a deep scar. L. Buberl (Münch. med. Woch., June 16, 1914).

Case of malignant pustule which was not arrested by local treatment. The patient's temperature continuing to rise, and his general condition to grow worse, 0.45 Gm. (7 grains) of **neosalvarsan** was injected into his veins; improvement occurred, immediately followed by recovery. Heim (Correspondenz-Blatt. für schweizer Aerzte, Sept. 30, 1916).

The fact that experiments have shown that **iphecacuanha** added to tubes containing 5 c.c. of broth invariably destroy the vitality of all the anthrax bacilli present, and no growth ensued (provided that they contained no spores), has suggested the use of this drug as a remedy.

In 18 consecutive cases of anthrax without a death, the writer's treatment consisted of surrounding the pustule at a distance of about $\frac{1}{2}$ inch, with a ring of hypodermic injections of 5 per cent. **phenol solution**, deep into the subcutaneous tissue; from 40 to 80 minims ($2\frac{1}{2}$ to 5 c.c.), in all, being employed. This is repeated each day for 3 or 4 days, when a **fomentation of powdered iphecac** (about 1 dram—4 Gm.—moistened with a little warm water) is applied and covered with oiled silk. The fomentation is repeated daily until the black slough begins to separate, after which **wet boric acid dressings** are used to expedite healing. Phillips (China Med. Jour., May, 1915).

Owing to the value of powdered **iphecacuanha poultices**, the writer has made a practice of carrying the iphecac in his first aid package and has used it as a poultice in 2 cases. The pustule stopped growing and became soft, with recovery as result. H. W. White (Jour. Amer. Med. Assoc., Sept. 23, 1916).

[This suggests that **emetine** given internally, as in amebic dysentery, *q.v.*, might

check anthrax where poultices of ipecacuanha prove inadequate or inapplicable where the surfaces involved are too great. EDITORS.]

Case in which all measures, including serum, had failed, the blood culture having revealed the presence of the organisms in the circulation. The following day, 100 c.c. ($3\frac{1}{2}$ ounces) of Dakin's **chloramin-T** and 80 c.c. ($2\frac{1}{2}$ ounces) of **antianthrax serum** were injected intravenously. In $\frac{1}{2}$ hour there was a severe chill, lasting 15 minutes, followed in a few hours by a fall in the fever and the pulse rate. A second blood culture was found negative and the patient progressed to a fairly rapid and a complete recovery. The local lesion was very slow in healing and 7 weeks after beginning recovery the leathery, black eschar which remained was removed by digestion with **papain**. Graham and Detweiler (Jour. Amer. Med. Assoc., Mar. 9, 1918).

Several sera are now obtained which appear to be of decided value in the treatment of anthrax. Of these the best known is **Scravo's**, which is obtained from the sheep or ass. The process consists in first immunizing the animals by **Pasteur's two vaccines**, and following this by repeated large injections of virulent cultures mixed with gelatin, which seems to obviate abscess formation. The serum has been largely used on the Continent, and several cures have been reported in England. The initial dose is 5 to 10 drams, repeated in twenty-four hours if necessary, or four or five 5-dram doses may be employed.

Case of anthrax treated by **Scravo's serum** in which recovery took place without excision of the pustule. Most cases of recovery after treatment by **Scravo's serum** have been treated by excision as well. W. M. Fergusson (Brit. Med. Jour., July 15, 1911).

At the instance of Kraus, various South American physicians, employed

heated normal beef serum in 146 cases with a mortality of but one death.

The writer's trials of **normal beef serum** in treatment of anthrax have confirmed in every respect the statements of Kraus and Penna as to its efficacy. It heated twice for $\frac{1}{2}$ hour at 56° C., it does not induce any injurious reaction when injected into man. He gave it subcutaneously in doses of from 10 to 30 c.c. in the 24 hours as a rule, sometimes giving more, up to a maximum of 60 c.c. The benefit was as prompt and as marked as with the prepared immune serum previously tried. Solari (Semana Medica, July 26, 1917).

Scravo reported a mortality of 6.09 per cent. in 164 cases treated with his serum, as compared with a mortality of 24.1 per cent. under other methods of treatment in Italy. Legge reported 12 English cases treated with **Scravo's serum**, with 2 deaths. Mendez of Buenos Aires, treated 1073 cases with his serum, which is presumably similar to **Scravo's** with a mortality of 4.19 per cent. The writers report 1 successful case treated with heated **normal beef serum**. Hyman and Leary (Boston Med. and Surg. Jour., Mar. 7, 1918).

In 200 cases of anthrax treated with **ordinary beef serum**, without other measures, the malignant pustule and septicemia subsided under it even more promptly than when anti-anthrax prepared serum is used. Before beef serum was used, the mortality had been 10 per cent. in 250 cases in the preceding 10 years, while with the beef serum treatment the mortality was only 0.5 per cent. in 200 cases. The serum was injected subcutaneously in doses of 30 or 50 c.c., repeated in 12, 24, or 36 hours as the case may require. In very severe cases, the serum can be given by the vein, previously sterilized by heating twice for $\frac{1}{2}$ hour at 56° C. Anaphylaxis is exceptional. Penna, Cuenca and Kraus (Prensa Medica, Apr. 10, 1918).

ERNEST LAPLACE,
Philadelphia.

ANTIMONY.—A grayish, tasteless, odorless, lustrous and brittle solid, generally classed as a metal because of its physical properties, though in certain of its chemical affinities it resembles phosphorus, a non-metallic element. Antimony compounds were formerly extensively used in therapeutics, but are now seldom employed.

The only official salt of antimony is the double tartrate of antimony and potassium (*antimonii et potassii tartras*), also known as tartar emetic, tartrated antimony, or stibiated tartar [$2K(SbO)C_4H_4O_6 + H_2O$]. This is made by the action of a boiling solution of potassium bitartrate on antimony trioxide.

PROPERTIES.—Tartar emetic occurs in the form of colorless, transparent crystals, which become opaque on exposure to the air, or as a white powder. It is without odor, but possesses a sweetish and at the same time acrid, metallic taste. It is soluble in 15.5 parts of water at 25° C. in 3 parts of boiling water, and in 20 parts of glycerin but insoluble in alcohol.

DOSE.—The dose of antimony and potassium tartrate ranges from $\frac{1}{30}$ grain (0.002 Gm.) to 1 grain (0.065 Gm.), the average expectorant dose being $\frac{1}{10}$ grain (0.0065 Gm.) and the emetic dose $\frac{1}{2}$ grain (0.032 Gm.).

PREPARATIONS.—The following official preparations, exclusive of the salt itself, contain tartar emetic:

Syrupus scillæ compositus (compound syrup of squill; Coxe's hive syrup), which, in addition to squill and senega, contains 0.2 per cent. of tartar emetic; dose, 30 minims (2 c.c., containing $\frac{1}{16}$ grain, or 0.004 Gm., of the antimony salt).

Mistura glycyrrhizæ composita (compound licorice mixture; brown mix-

ture), containing extract of licorice, camphorated tincture of opium, sweet spirit of niter, and 6 per cent. of wine of antimony; dose, 2 fluidrams (8 c.c., containing approximately $\frac{1}{32}$ grain, or 0.002 Gm., of tartar emetic).

Wine of antimony was formerly official as a 0.4 per cent. solution of tartar emetic in white wine; dose, 15 minims (1 c.c., containing $\frac{1}{16}$ grain, or 0.004 Gm., of tartar emetic).

MODES OF ADMINISTRATION.—Tartar emetic is best administered in solution, with its metallic taste disguised by some flavoring agent, such as syrup of orange peel. The more dilute the solution given, the greater likelihood of the production of a cathartic effect. An ointment of tartar emetic (1 part in 4) was formerly official, but the disagreeable effects of antimony locally have caused its external use to be largely abandoned.

INCOMPATIBILITIES.—Tannic acid and salts of silver and lead precipitate antimony compounds from their solutions.

CONTRAINDICATIONS.—In all cases which show a tendency to cardiovascular depression or marked general adynamia, antimony compounds should be avoided. In the aged, as well as in children, they should be used only with circumspection, and in small doses.

PHYSIOLOGICAL ACTION.—

Local Effects.—Tartar emetic exerts an irritating effect when applied locally. If left in contact with the skin for several days it causes local hyperemia and pain, soon followed by an eruption of small papules, arising from the dermal glands and hair follicles. The lesions soon become transformed into vesicles and

ultimately into large pustules. Considerable local pain is likely to be present. If the application be not discontinued, ulceration and sloughing of the superficial tissues may ensue. The irritation caused by tartar emetic is due not to the double salt itself, but to simple salts of antimony formed through the decomposition of the double compound by the acid skin secretions (Sollmann).

General Effects.—*Nervous System.*

—Small single doses of tartar emetic do not exert any appreciable nervous effect. Large amounts diminish or abolish sensation by depressing the sensory columns of the spinal cord. Although the motor side of the cord may also be to a certain extent depressed, this effect is secondary to that on the sensory portion, as shown by the fact, recorded by certain experimenters, that voluntary movements may occur in frogs poisoned with antimony after the spinal reflexes have been paralyzed. In man it is not known how much of the spinal depressant effect is due to direct action of the drug on the nerve-cells, and how much to circulatory disturbances.

Circulation.—Antimony is a direct depressant to the heart. Even moderate doses exhibit eventually a tendency to slow and weaken the pulse, though the preliminary emetic action is generally attended with a temporary increase in the rate. The blood-pressure shows a gradual fall under antimony, partly owing to the cardiac weakening, but in considerable measure, it is believed, because of vascular dilatation. It appears to be established that antimony depresses directly the muscular walls of the vessels, as it does the cardiac

musculature. Whether depression of the vasomotor center is likewise a factor in the fall of blood-pressure has not as yet been definitely ascertained. According to Sollmann, who assimilates the circulatory effects of antimony to those of arsenic, the capillary vessels are also paralyzed by this drug, their walls becoming more permeable,—a fact which accounts for the diarrhea after full doses, further favoring a reduction in the blood-pressure. Circulatory depression under antimony compounds may also be produced as a sequela to the emesis.

Respiration.—The respiratory center is but little influenced by antimony except in cases of poisoning, when it is manifestly depressed. In the early stages, and with small doses, various relatively unimportant changes in the breathing rate take place indirectly as a result of nausea and circulatory depression.

Alimentary Tract.—Taken internally in full doses, tartar emetic induces nausea and vomiting, an effect generally considered to be due chiefly, if not wholly, to irritation of the gastric mucosa. These symptoms also appear upon hypodermic or intravenous injection of the drug, but larger doses must be used in order to produce them than are required upon oral administration. Ordinary doses of tartar emetic do not seem to alter the appearance of the gastrointestinal mucous membranes; larger amounts induce marked congestion of the membranes and exfoliatory diarrhea, as in arsenic poisoning or Asiatic cholera. The irritation caused by tartar emetic in the stomach has been ascribed, like that produced when it is applied exter-

nally, to decomposition of the double salt into a simple antimony salt by the acid of the gastric juice; this probably does not account wholly, however, for the irritant effect, as similar irritation is produced by the drug in the intestine, the juices of which are alkaline in reaction.

The vomiting induced by antimony compounds is accompanied, like that resulting from the ingestion of other emetics, by free perspiration, an increased flow of saliva, and general depression.

Large doses of antimony also cause intestinal irritation, with the production of a more or less profuse and watery diarrhea, often accompanied by colic.

Secretions.—Antimony compounds exert no direct effect on the secreting organs. The nauseant effect of small doses, however, leads indirectly to an increase in the salivary discharge, perspiration, and mucous secretions of the respiratory tract. Variable and relatively insignificant alterations may occur in the secretion of urine, which may be either increased or diminished.

Temperature.—The temperature is not appreciably influenced by ordinary doses of antimony. After doses sufficient to produce violent emesis, the temperature of the extremities may be distinctly lowered (Ackermann). Toxic doses cause a pronounced general hypothermia.

ABSORPTION AND ELIMINATION.—Antimony is rather promptly absorbed from the gastrointestinal mucous membranes, though not with quite the same rapidity as arsenic. It is also readily absorbed from abraded surfaces; cases of fatal poisoning have occurred in this way.

After absorption the metal tends to accumulate in the liver. Its paths of excretion lie through the kidneys, alimentary tract, and in less degree through the respiratory mucous membranes, the salivary and mammary glands, and the skin.

UNTOWARD EFFECTS AND ACUTE POISONING.—Excessive doses of antimony compounds produce an exaggeration of the ordinary emetic effect. Vomiting is violent and persistent, may become bloody, and is attended with intense prostration. There is marked thirst, and a sense of constriction in the throat. Pains in the abdomen and diarrhea also occur, the fecal discharges becoming serous, *i.e.*, of the choleraic type. Cramp-like pains in the extremities may occur. The bronchial secretions may be greatly increased. Symptoms of collapse soon make their appearance. The pulse, at first often accelerated, becomes slow and feeble. The respiration is likewise depressed, the skin bathed with perspiration and more or less cyanosed, the muscles relaxed, and the temperature lowered. The urine may be increased at first; later it is scanty, albuminous, and perhaps bloody. A period of stupor, terminating with feeble convulsive movements, may precede death. The period required for the completion of fatal poisonous effects ranges from one hour—the shortest lethal period on record—to several days. In patients still alive on the third, fourth, or fifth day, a pustular eruption may appear.

In rare cases the gastrointestinal symptoms, especially the vomiting, are said to be totally absent, collapse and delirium being the more prominent features.

The lethal dose of antimony cannot be definitely stated. One patient is said to have succumbed to 2 grains (0.13 Gm.) of tartar emetic, while doses of several hundred grains have been recovered from, doubtless in part owing to the thorough emesis produced. According to Reese, 20 to 40 grains (1.3 to 2.6 Gm.) represent about the fatal dose. Even relatively small doses of antimony compounds may prove harmful in conditions associated with cardiac weakness. The direct depressing action of the drug on the myocardium easily leads to a slowing and weakening of the heart action, but a reflex inhibitory effect through the vagus may also be considered in part responsible for cardiac arrest under antimony (Pouchet). The combined cardiac and vasomotor depression in cases of poisoning leads to a marked fall of blood-pressure and hyperemia of the venous side of the circulatory system.

The changes found *post mortem* consist chiefly of intense hyperemia of the gastrointestinal tract and other viscera, especially the liver and lungs. The mucous membranes of the stomach, bowels, and respiratory tract are usually reddened and covered with blackish secretions. The lungs may show points of hemorrhage, as well as areas of emphysema or atelectasis. The liver is softened, and the brain is likely to present apoplectic foci. The blood is said to remain uncoagulated. In some cases—probably those with a rapid fatal ending—the gastrointestinal changes have been wanting.

Case of erysipelas of the face associated with insomnia and general prostration in a vigorous young man in whom the administration of 1½ grains (0.10 Gm.) of tartar emetic

proved fatal. The autopsy revealed hepatic enlargement, marked congestion and points of hemorrhage in the intestine from the jejunum to the upper part of the colon, and a fatty appearance of the liver, spleen, and myocardium. G. Pouchet (*Précis de pharmacol.*, p. 651, 1907).

TREATMENT OF ACUTE ANTIMONIAL POISONING.—Tannic acid, most easily obtainable in the form of tea, should be freely given to precipitate the antimony still in the stomach. If vomiting is present the precipitated tannate will be spontaneously ejected, especially if mucilaginous fluids are administered to assist in the clearing out; if there is no vomiting at the time, the precipitate should be washed from the stomach with a **stomach tube**. Soluble **magnesium** or **calcium salts** may also be used as precipitants. A purge may be given to remove the metal as promptly as possible from the intestinal tract. Symptomatic relief is afforded by **opium** or **morphine**. Collapse should be combated with **strychnine**, **caffeine**, **digitalis**, **camphor**, etc., and the application of **external heat**. **Demulcent drinks** are useful to soothe the irritated mucous membranes during the period of recovery.

CHRONIC POISONING.—Chronic antimonial poisoning is comparatively rare. The symptoms in many respects resemble those of acute poisoning. Meierhofer and Nobling experimentally took 1 mg. ($\frac{1}{100}$ grain) of tartar emetic daily, gradually increased to 1 cg. ($\frac{1}{10}$ grain), for two weeks. The early symptoms noted included: sensation of weakness in the limbs and pains in the joints, chilliness, salivation, thirst, inner feeling of warmth, som-

nolence, nightmares, frequent and irregular pulse, vertigo, pallor. Later there appeared anorexia, * nausea, colicky pains, dysphagia, dyspnea, precordial pain, diarrhea alternating with constipation, polydipsia resulting in diuresis, weak and slow heart action, hepatic engorgement and pain, prostration, albuminuria, and a loss in body weight amounting to 3½ kg. (over 7 pounds). Two months were required for complete disappearance of the phenomena of intoxication (Pouchet). Pustular eruptions are also sometimes observed after continued use of antimony preparations.

THERAPEUTICS.—As an Expectorant.—Antimony compounds are still used to a certain extent for the purpose of increasing the secretions, especially the discharge of mucus in the respiratory passages in catarrhal inflammations associated with excessive local dryness and cough. The outpouring of fluid produced is a result of the nauseant effect of the drug; in this respect antimony is preferable to any other metal in that only about one-tenth the emetic dose is required to induce nausea (Sollmann). The dose of tartar emetic as expectorant in the early stages of **acute bronchitis** or **laryngitis** in adults is about $\frac{1}{10}$ grain (0.0065 Gm.). In the later stages, when free secretion is present, antimony is no longer suitable. It is not infrequently administered in the form of the official compound syrup of squills, dose 30 minims (2 c.c.); or the wine of antimony, dose 15 minims (1 c.c.). Other preparations, used chiefly on the continent of Europe, include the so-called "kermes mineral," or sulphurated antimony,—a mixture of the

oxide and sulphide of antimony with acid antimonite of sodium,—dose 1 to 4 grains (0.065 to 0.25 Gm.), and the white oxide of antimony, or acid potassium antimoniate, used in even larger doses. While the last-named preparations are credited with exerting a milder, more gradual effect than tartar emetic, they have the disadvantage of being insoluble in water and depending in part for their absorption upon the hydrochloric acid present in the alimentary tract; their absorption is, therefore, subject to variation with a resulting probability either of inefficiency of the drug or of excessive action and vomiting.

In view of the possible depressing effect of antimony compounds upon the circulation it is perhaps advisable to combine some cardiovascular stimulant with them. Thus, Pouchet writes the following:—

℞ *White oxide of antimony* 7½ grs. (0.50 Gm.).
Tincture of digitalis 6 grs. (0.40 c.c.).
Syrup of orange flower 2 fl. oz. (60 c.c.).

M. Sig.: One tablespoonful every two hours.

In the later stages of catarrhal inflammations, when free secretion is present, antimony compounds are no longer advisable.

Antimony and potassium tartrate is a remedy of great value. To obtain free secretion from the mucous surfaces and the skin, antimony remains pre-eminent. It should always be prescribed in small doses given frequently. Only by this means can its full effect be obtained without danger of giving rise to depression. In **bronchial catarrh** and **bronchitis** there is no drug to take its place. Great severity in the attack is no bar to the use of the drug. In the early stage of **bronchopneumonia** in children it is of undoubted value, being

most useful at the period when the consolidation is still in patches. Belladonna is also of value at the same period, and the two remedies may be combined. **Laryngismus stridulus** is another disease in which antimony is of great benefit; it should be given as wine of antimony in doses of 15 to 20 drops (0.9 to 1.2 c.c.), so as to induce a slight feeling of nausea. Smith (Brit. Med. Jour., Feb. 29, 1908).

As a Diaphoretic.—Antimony compounds, likewise by reason of their nauseant effect, are capable of producing sweating, and were formerly so used to a considerable extent. In view of the fact, however, that other more efficient and less depressing diaphoretics—pilocarpine in particular—are available, there appears to be practically no occasion for the use of antimony in this direction.

As an Emetic.—Conditions are much the same in respect to the use of antimony as an emetic. The full doses—such as $\frac{1}{2}$ grain (0.03 Gm.) of tartar emetic—required to produce emesis are particularly likely to bring on unwelcome cardiovascular and general systemic depression. Further, the drug has the disadvantage of acting more slowly than apomorphine, zinc or copper sulphate, and ipecacuanha. In cases of **poisoning** unattended by cardiovascular depression, the use of a combination of ipecac with tartar emetic is sometimes recommended, the former drug supplying the promptness of action which the antimony compound lacks, while the latter adds to the effectiveness of the emesis and prolongs it.

Smith finds the wine of antimony in doses of 1 or 2 minims (0.06 or 0.12 c.c.) a useful addition to the prescription in cases of gastric derangement. It acts, in his opinion,

on the principle that all nauseating medicines, given in minute doses, lose their irritating properties and become gastric sedatives.

As a Cardiovascular Sedative.—At the start of acute infections, particularly in **pneumonia**, tartar emetic was formerly administered in large doses for the purpose of lowering vascular tension and thereby antagonizing congestion of the affected part. It was also claimed, in the case of pulmonary affections, that the sudden more or less forcible movements attending the act of vomiting, by exerting mechanical pressure upon the lungs, favored the circulation of blood in the lung-vessels and forestalled stasis. In addition, the purgative and nervous sedative effects were also regarded with much favor. The drug was likewise freely used in pulmonary tuberculosis, acute rheumatism, and a host of other affections. More recently it has become quite clear that these supposed advantages are more than offset by the almost universal depressant tendency of the drug. While the symptoms may at first appear to be in part relieved, the succeeding stage of cardiovascular depression, sometimes even amounting to collapse, generally leaves the patient in a worse position to resist the disease process than he would otherwise have enjoyed. The apparent state of tolerance to antimony established by repeated use of large doses has been shown to amount merely to a condition of lowered tone of the nervous system, whereby the usual stimuli leading to the production of vomiting and other characteristic effects completely lose their influence. The use of antimony as a cardiovascular sedative has,

therefore, been abandoned by nearly everyone, though a few still make use of it in small doses in the **early** stages of pneumonia. *Veratrum viride* and aconite are preferable to antimony compounds where this indication is to be met. In **malarial remittent fever** Frances recommended the use of tartar emetic in cases with highly congested face and violent headache.

Tartar emetic a remedy of almost specific properties in capillary **bronchitis** and **bronchopneumonia**. It is best first to withdraw 200 to 250 Gm. ($6\frac{1}{2}$ to 8 ounces) of blood and then to give a tablespoonful of a solution containing 40 cg. (6 grains) of the drug to 150 Gm. (5 ounces) of water. With a moribund and cyanosed patient with thready pulse, supervision must be very careful and the administration should be stopped as soon as vomiting or diarrhea appears, or when dyspnea increases, collapse supervenes, or the surface becomes cool. Opiates should not be prescribed at the same time. It is rare that tartar emetic can be given through an entire day. Generally one must stop and begin again the day after, but with smaller doses. After the severe symptoms have disappeared, the white oxide of antimony does good service in aiding expectoration. While antimony is excellent in forms of pneumonia where there is a tendency to suffocation, it is a mistake to employ it as routine treatment in this disease. A. Robin (*Bull. gén. de thérap.*, Aug. 15, 1903).

In **trypanosomiasis** antimony has been found frequently to give excellent results. It has been administered by the mouth, and by intravenous, intramuscular, or subcutaneous injection. The latter two methods, however, appear to be impracticable, owing to the severity of the local reaction induced. The intravenous method is the most efficient.

In a series of experiments on trypanosome-infected rats to determine the therapeutic value of antimonial compounds, the writers found that, although the antimony salt of succinic acid is capable of causing the disappearance of trypanosomes, yet in the vast majority of cases its action is of very short duration. It is irritant locally, more toxic than the sodium antimony thioglycollate or the triamide of antimony thioglycollic acid, and much less efficient in the treatment of experimental trypanosomiasis. Rowntree and Abel (*Jour. Pharmacol. and Exper. Therap.*, July, 1911).

A **stable colloidal antimony** may be prepared by the following method: A current is passed in sparks from an induction coil, and an eight volt accumulator between two aluminum foil electrodes immersed in chloroform containing coarse particles of metallic antimony. The antimony passes into a powdery state and some goes into solution. When the chloroform is distilled off a tardy residue of colloidal antimony is left. This can be dried in a desiccator, in air, or even over a Bunsen burner without materially affecting it. Colloidal antimony was found by the author to possess remarkable therapeutic power in protozoal diseases. U. N. Brachmachari (*Lancet*, Oct. 21, 1916).

In **certain skin diseases**, including **eczema** and other inflammatory states, antimony in small doses has been recommended as a substitute for arsenic. The experience with it as yet has been insufficient, however, to permit of accurately defining its relative value.

In **anemia** antimony has also been praised as a substitute for arsenic.

Antimony is an excellent hematinic. It increases the number of red blood-cells and the percentage of hemoglobin, and also enhances the resistance of the red cells, as does arsenic. The improvement in the

blood after antimony persists for some time after the drug has been discontinued. Large doses, however, produce hemolysis. Montemagno (Gaz. degli Ospedali, Dec. 4, 1904).

Externally, antimony compounds have been applied to the skin to obtain prolonged counterirritant effects. Their tendency to cause eruptions and even destroy the tissues locally constitutes a marked disadvantage of its local use.

Unna has recommended a solution of chloride of antimony (about 30 per cent.) as a local remedy in **lupus**, claiming that it has a selective affinity for the tuberculous nodules. Beneficial effects in other cutaneous diseases, including **psoriasis**, have also been reported.

Solid chloride of antimony found to be strongly caustic and escharotic, owing to its affinity for water. Kept in contact with the skin for some time it is decomposed, with the production of hydrochloric acid and antimony oxychloride; this action takes place at once when the drug is applied to an ulcer or the skin is broken. With a solution of antimony chloride there is no such strongly caustic effect unless the solution is continuously applied. It will frequently exert, however, a beneficial action on inflamed skin. In a case of **psoriasis** the application of solid antimony chloride with a glass rod checked the inflammation without causing the formation of a scab. In 2 cases of **lupus** of the face the normal skin was not attacked by the solution, while the diseased parts were beneficially influenced by it. A. M. McDonald and J. R. Hill (Pharm. Jour., Jan. 25, 1908; Lancet, Feb. 29, 1908).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

ANTIPYRIN. — This substance, official in the U. S. Pharmacopœia as *Antipyrina*, and in the British Pharmacopœia as *Phenazonum*, is an organic base obtained by the condensation of acetoacetic ether with phenylhydrazine, and methylation of the compound thus produced by means of methyl iodide. The constitution of antipyrin is expressed by the chemically descriptive term Phenyl-dimethylpyrazolon, and its formula is $(C_6H_5)N.N(CH_3).C(CH_3):CH.CO$. It is also sometimes known as Analgesin.

PROPERTIES. — Antipyrin occurs as a fine, white, crystalline powder. It has no odor, but is slightly bitter in taste. It is distinguished from the other official coal-tar antipyretics—acetanilide and acetphenetidin—by its ready solubility in water, 1 part of antipyrin dissolving in less than an equal weight of water. It is soluble in 1 to 2 parts of alcohol, 1 to 2 parts of chloroform, and 30 to 50 parts of ether, according to the temperature.

DOSE.—The dose of antipyrin for adults is 5 to 10 grains (0.3 to 0.6 Gm.); 15-grain or even larger doses were formerly often given, but in late years it has been recognized that such dosage is excessive and unnecessary. Doses larger than $7\frac{1}{2}$ grains (0.5 Gm.) cannot be considered safe, and this dose should not be repeated for four hours (Mayor). To children, who bear the drug well, as many grains of antipyrin may be given as there are years of age, until the adult dose is reached.

Out of 150 physicians using antipyrin, only 23, or 15.3 per cent., exceeded a dose of 10 grains (0.6 Gm.), while 66, or 44 per cent., never exceeded a dose

of 5 grains (0.3 Gm.); 109, or 72.6 per cent., employed 5 grains (0.3 Gm.) or less as a minimum dose. Kebler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 126, July 3, 1909).

MODES OF ADMINISTRATION.

— Antipyrin may be given either in powder form or dissolved in water. The latter method is preferable, as the local irritant effect of the drug on the gastric mucosa is thereby minimized. If it cannot be taken except in a capsule, the patient should take a quarter- or half- glassful of Vichy water immediately after (Clement). Whenever practicable, the drug should be taken with or after meals. The bicarbonates of sodium or potassium may be combined with antipyrin with advantage, as they tend to neutralize, through their alkalinity, the effects of any products of decomposition which may be formed in the stomach by the action of the gastric juice on the drug. BrisseMORET recommends the following plan of administering antipyrin: A tablespoonful of a mixture consisting of antipyrin, 4 Gm. (1 dram); sodium bicarbonate, 2 Gm. ($\frac{1}{2}$ dram); simple syrup, 15 Gm. (4 drams), and distilled water, 45 Gm. ($1\frac{1}{2}$ ounces), is first taken, and is at once followed by a like amount of the following: Citric acid, 2 Gm. ($\frac{1}{2}$ dram); distilled water, 50 Gm. ($1\frac{2}{3}$ ounces), and syrup of limes, 15 Gm. (4 drams). Carbon dioxide is liberated in the stomach, mitigating the local irritant effect of antipyrin, and potassium carbonate is subsequently formed from the citrate, counteracting any deleterious effect which the drug may tend to exert on the blood. A simpler plan for giving antipyrin in an effervescent preparation is to dissolve the

drug in some water containing carbonates, such as Vichy, and add citric acid. Coffee has been recommended by Batterbury as a good vehicle for antipyrin; its taste is thereby almost entirely disguised.

INCOMPATIBLES. — Antipyrin is incompatible with many substances. As already stated, it is an organic base, and, therefore, reacts with the whole series of alkaloidal precipitants. It is thrown down from concentrated solutions by pure phenol, by tannic acid and drugs rich in it (catechu or gambir, kino, hamamelis, cinchona, rheum, rose leaves, uva ursi); by solutions of salts of mercury, lead, and copper; by compounds of arsenic and antimony, by tincture of iodine, and by alkalies. When rubbed up with chloral hydrate or with sodium salicylate it forms an oily liquid.

It is decomposed by betanaphthol and potassium permanganate, and when combined with sodium bicarbonate is said to disengage the odor of ether. Nitrites, including spirits of nitrous ether, cause a green color to develop when added to dilute solutions of antipyrin, owing to the formation of a nitrosoantipyrin; in concentrated solutions a green crystalline precipitate is formed. Ferric chloride colors antipyrin solutions red; ferrous phosphate, yellow-brown; ammonia alum, dark yellow; hydrocyanic acid, yellow; nitric acid, pale yellow, and fuming nitric acid, green. Combination of antipyrin with calomel has been warned against, in view of the possible formation of a dangerous amount of corrosive sublimate (Werner, Robinson). Especially is such a combination with the further addition of sodium bicarbonate to be avoided.

If a prescription calling for 2 grains (0.13 Gm.) of calomel, 6 grains (0.39 Gm.) of antipyrin, and 12 grains (0.77 Gm.) of bicarbonate be taken *in toto* by a patient, that patient would receive a soluble mercury salt equal to $\frac{1}{8}$ or $\frac{1}{2}$ grain (0.021 or 0.032 Gm.) of corrosive sublimate. If administered in capsules the danger would be somewhat less, as the gastric acidity would tend to neutralize the sodium bicarbonate, on the presence of which the reaction depends. Report from Association Laboratory (Jour. Amer. Med. Assoc., Jan. 28, 1911).

Antipyrin is also incompatible with benzoates, orthoform, resorcin, thymol, pyrogallol, ethyl carbamate, and chromic acid.

The precipitation of antipyrin in the presence of iodine has been suggested by Maragliano as a test for minute quantities of the drug; 5 drops (0.3 c.c.) of Lugol's solution added to 6 c.c. (97 minims) of acidified urine will cause a reddish precipitate to form.

CONTRAINDICATIONS.—In patients with greatly weakened hearts or marked general enfeeblement, and in persons of advanced age, antipyrin is relatively unsafe, owing to the possibility of its inducing cardiac depression, as well as lowering the blood-pressure through excessive vascular dilatation. According to Huchard, antipyrin is contraindicated in all cases of renal disease, since its elimination is then interfered with, and unexpected toxic effects may develop. More especially does this hold in febrile states—pneumonia, typhoid fever, tuberculosis—complicated by nephritis. Spanoudis found persons suffering from erysipelas peculiarly susceptible to antipyrin; it usually caused anuria and a profound fall of temperature.

PHYSIOLOGICAL ACTION. —

As Antipyretic.—Antipyrin was introduced into medicine as a reducer of fever in 1884, and was soon found to be more effective and less dangerous than any other drug previously discovered. Doses of 10 or 15 grains (0.6 to 1.0 Gm.) produce, provided pyrexia be present at the time, a fall of temperature of from 1° to 5° F. (0.5° to 2.8° C.). According to Manquat, this effect begins one-half hour after the ingestion of the drug; in about four hours (the period varying according to the cause of the febrile process) the temperature commences to rise again.

The cause of the antipyretic effect of antipyrin has given rise to many investigations and discussions—by no means always concordant. In experimental animals, as in man, a reduction of temperature takes place—when small (therapeutic) doses are used—only in the presence of pyrexia, the normal temperature being uninfluenced. Massive (poisonous) doses are required to produce a like effect under normal conditions.

In the calorimetric experiments of Wood, Reichert, and Hare, dogs rendered febrile by injections of pepsin showed, under the influence of antipyrin, a decrease in both heat production and heat dissipation. The former effect usually exceeded the latter; hence, the body temperature fell. Destrée obtained similar results. Cerna and Carter, on the other hand, witnessed a pronounced increase in heat dissipation in addition to the diminution in heat production. According to Gottlieb, the reduction of temperature is due exclusively to increased heat dissipation, heat production remaining unaffected; this view

is, however, at variance with the accepted theory. As for the portion of the organism acted upon in the production of the antipyretic effect, evidence clearly points to the basal ganglia of the brain, and in particular to the region of the corpus striatum. The experiments of Sawadowski showed that, if the connections of these nerve-centers with lower nervous structures are cut, neither the coal-tar drugs nor injections of fever-producing substances cause any change in the temperature, whereas, if their superior connections are severed, the usual characteristic effects appear. In recognition of this fact it is now generally accepted that the action of antipyrin takes place through the heat-regulating centers located in the portion of the brain already mentioned. The formation of body heat is influenced by virtue of the control over muscular activity vested in these centers, while the output or dissipation of heat is altered through similarly regulated changes in the peripheral blood-vessels. Diminished muscular activity leads to lessened heat production, whereas dilatation of the peripheral vessels leads to increased heat loss through exposure of a greater amount of blood to the cooling influence of the surrounding air and increased evaporation of sweat. In agreement with this view as to the mode of action of antipyrin (at least with respect to heat dissipation) is the fact that often, clinically, the fall in temperature is accompanied by more or less profuse sweating, seen first about the forehead or neck, later upon the chest and face. The rise of temperature, taking place as the effect of the drug wears off, is not uncommonly at-

tended with chilly sensations and shivering. Sweating is generally considered to be more marked after the use of antipyrin than after acetanilide or acetphenetidin. It has been advised that this effect be antagonized with atropine; under these circumstances we should expect, however, the antipyretic effect to be interfered with.

The cerebrum and corpus striatum were removed from 18 rabbits. In 9 of these cases, being those exhibiting as a rule the fewest anatomic complications, a subnormal body temperature (32.5° to 37.5° C., the morning after operation) resulted. The remaining 9 animals (besides 2 of the first mentioned 9, for the first 4 days after operation) behaved essentially like normal animals. The hypopyrexia animals showed signs of collapse, asymmetrical muscular disturbances, peripheral vasoconstriction and slow respiration. Their temperature condition was not due to cold, starvation or hemorrhage, but to a disturbance of central heat regulation, probably seated chiefly in the corpus striatum. When given 0.1 to 0.4 Gm. (per kilo) antipyrin they showed a definite rise in temperature rather than a fall, and a conspicuous absence of the vasodilation usually seen after the drug, as well as of the hyperpnea which would be expected from the larger doses within this range. Muscle stiffness was in evidence, bordering, with the larger doses, on tonic and clonic convulsions. Barbour and Deming (Jour. of Pharmacol. and Exper. Therap., Nov., 1913).

Action as Analgesic.—The mode of action of antipyrin in relieving pain is still somewhat uncertain. The fact that this drug, in common with other coal-tar antipyretics, sometimes causes more or less drowsiness while exerting its effect would seem to indicate the presence of some sedative action on the nerve-centers. In-

deed, one view hitherto prominently entertained has been that the drug depressed in particular the sensory cells located in the thalamic region. The more recent studies, however, have made it seem probable that intracranial vasomotor changes are at least partly responsible for the analgesia.

Wiechowski, in 1902, performed experiments the results of which supported this conception, and, in 1909, Weber, with the aid of an improved experimental method, showed quite clearly that antipyrin, administered to animals by intravenous injection, caused, after brief preliminary dilatation, prolonged constriction of the intracranial vessels. Taking for granted the fact that similar results will obtain upon ingestion of antipyrin in man, it seems reasonable to presume that, at least in the relief of headache, antipyrin acts by inducing intracranial vasoconstriction.

The effects of antipyrin on the nervous system as a whole may be described briefly as follows: There occurs at first a mild degree of narcosis, betokened by slight somnolence, diminished reflex excitability, and lessened sensibility to pain. (Even before this, according to Pouchet, there may appear, with full doses, a brief period of excitation, attended, in man, with increased mental activity, loss of fatigue sensations, and even, occasionally, a species of dreaminess or actual "intoxication.") Succeeding the period of depression appears a stage characterized especially by exaggerated reflex response. If the dose be large enough, convulsive movements even appear, which are believed to be due to excitation both of the lower brain-centers and spinal cord,

since either clonic or tonic spasms—the former typically bulbar and the latter strychniform—may predominate. Finally, there occurs a stage of general motor paralysis and anesthesia, due to depression of the entire central nervous system by the drug.

The peripheral nerves, especially the sensory, are depressed by antipyrin when it is applied to exposed nerve-trunks or taken internally in large amounts. It is considered extremely doubtful, however, whether antipyrin in the doses employed in therapeutics can exert any noteworthy portion of its analgesic effect in this manner; the central nervous effects appear always to predominate over the peripheral.

The respiratory center in the medulla is apparently at first stimulated by antipyrin, the rate of respiration being increased. Later, with poisonous doses, there occurs paralysis of this center.

Action on the Circulation.—Antipyrin in moderate doses has been shown to cause a rise in the blood-pressure. With toxic doses the rise is soon followed by a pronounced fall. The primary rise is believed to be due in part to direct cardiac stimulation; but vasomotor changes are also probably involved. According to Gley and Caravias, antipyrin causes, in addition to dilatation of the peripheral vessels, constriction of the vessels innervated by the splanchnics, the net result being a rise in the general blood-pressure. The larger the dose, the more marked are both of these effects. With large doses, in addition, cardiac slowing and enfeeblement begin to appear, the blood-pressure, however, varying but little. Finally, under toxic doses both vasomotor centers and heart become pro-

gressively paralyzed, and a marked secondary fall of blood-pressure is seen (Pouchet).

On the blood antipyrin, even in large amounts, exerts practically no deleterious action—a feature distinguishing this drug both from acetanilide and, to a certain extent, from acetphenetidin. Though Lépine claimed to have observed methemoglobinemia in antipyrin poisoning, many authors seem disposed to deny antipyrin any methemoglobin-forming power. Lépine's opinion, however, is far more reliable. According to Sollmann, medium-sized doses of antipyrin merely render the oxygen of the oxyhemoglobin less labile—an effect doubtless sufficient to account, at least in part, for the cyanosis sometimes observed after the use of this drug.

Action on Secretions.—Certain secretory functions are interfered with by antipyrin (Pouchet). The renal vasoconstriction produced by the drug may reduce the flow of urine—a fact emphasized by Huchard. The sweat secretion may, however, so increase as to make up, to a certain extent, for the deficiency of renal elimination. The mammary secretion, according to Pouchet, is greatly reduced by antipyrin.

Action on Metabolism.—Antipyrin used in moderately large amounts has been shown by Umbach, Robin, and other investigators to lessen the metabolism of nitrogenous compounds in man. The urinary elimination of urea in particular is diminished; that of uric acid, on the contrary, may remain unaltered or be increased. Incompletely oxidized sulphur and phosphorus compounds exhibit an increase, another evidence of the fact that the drug hinders oxidation and catabolic changes in general.

Lépine showed that antipyrin led to a diminished consumption of sugar in the capillaries and lessened glycogen transformation. While these statements represent the prevailing view as to the action of antipyrin on metabolism, it must be stated that in certain experiments, especially those of Crolas and Hugounenq and of Cazeneuve, which were carried out in dogs, the elimination of urea was sometimes found to be increased instead of diminished, and that certain authors are disposed, therefore, to consider the question as not yet having been definitely settled, or, like Cushny, to accord but little significance to the effects of antipyrin in this direction. In any case antipyrin here diverges considerably from acetanilide, the power of which in large doses to increase markedly the elimination of nitrogenous wastes has been clearly established.

Local Effects.—Externally, antipyrin has analgesic, vasoconstrictor, and antiseptic properties. It is mildly irritating when applied to mucous membranes, and if injected subcutaneously may induce necrosis of tissues and abscess formation. The analgesic and vasoconstrictor (hemostatic) effects are best obtained with 30 or 40 per cent. solutions (Wood). According to Saint-Hilaire, complete anesthesia of mucous membranes may be obtained with antipyrin in 30 per cent. strength. As an antiseptic the drug is capable, in 10 per cent. solution, of inhibiting the growth of certain pathogenic bacteria. According to Roux and Rodet, the *B. coli communis* is distinctly antagonized by it in 4 per cent. strength. Putrefactive processes are completely arrested by even weaker solutions. Weak solu-

tions of antipyrin also interfere with peptic and diastatic enzyme action.

Absorption, Fat, and Elimination.

—Antipyrin is rapidly absorbed from the gastrointestinal tract. In the dog it has been found to be in part oxidized in the system. In man it appears in the urine, according to Lawrow (1901), in the form of a double glycuronic acid, in which antipyrin itself is probably held in the form of an oxyantipyrin. Its chief route of elimination is by the kidneys, but it has also been detected in the saliva, the sweat, and the milk of nursing women. It begins to appear in the urine in three-quarters to one hour after ingestion, according to Perret and Givre; in five to twenty-five minutes, according to Pouchet. The elimination is not complete until after about thirty-six hours in adults, but is claimed to occur more rapidly in children.

Given in large doses,—in 2 capsules each containing 15 grains (1 Gm.), at intervals of two hours,—antipyrin may be detected in the milk, according to Fieux, in from five to eight hours after its ingestion, while from nineteen to twenty-three hours afterward none can be found; hence, its elimination lasts eighteen hours at the maximum. It passes into the milk only in a very low proportion—very much less than 50 mg. ($\frac{1}{2}$ grain) in 1000 Gm. (1 quart) of milk. It is only under exceptional conditions—*e.g.*, when 60 grains (4 Gm.) are administered in sixteen hours—that it may reach this proportion. It does not influence in any way the quality of the milk. The secretion remains very abundant, provided the woman continues to nurse. From the absence of general symptoms and from examinations of the weight, the infinitesimal quantity absorbed by the nursing does not seem to have any unfavorable action.

Antipyrin appears in the urine, according to Lamanski and Main, forty minutes after being taken by the

mouth and thirty minutes after its introduction into the rectum.

Any of the substances producing coloration when added to aqueous solutions of antipyrin may be employed in testing the urine for it. Ferric chloride, however, is most generally employed for the purpose, revealing, by the red color produced, the presence of the drug in dilutions as high as 1:100,000.

Untoward Effects. — Under this heading will be considered those accidents which follow the use of antipyrin in therapeutic doses in a certain percentage of cases. It has repeatedly proven poisonous unexpectedly in persons accustomed to its use, even in small doses. Blebs about the mouth and gums have been observed. The penis and scrotum may also show a vesicular eruption which sometimes form scabs, or become cyanotic. It may cause twitchings.

Case of bullous eruption in the buccal cavity due to the ingestion of antipyrin. The writers call attention to the possibility of such eruptions being limited exclusively to this region. Nicolas and Moutot (*Ann. de Dermat. et de Syph.*, No. 11, 1911).

After taking 1 dose of 0.75 Gm. (12 grains) of antipyrin salicylate a colored man of 40, burning and edema was complained of to such an extent that it seemed that a caustic had been taken by mistake. Unaware that the drug caused the trouble, he took another dose. By the next day the lips and mouth looked as if lined with yellow cotton, and in two days the tissue affected was cast off, the cheeks, lips, gums and pharynx being thus denuded, and the whole course of the esophagus smarted and there was also pain in the epigastrium, whenever the man took any water or milk, the only things allowed. The ulceration was apyretic and healed in the course of two weeks without leav-

ing a trace. Two years before the man had had a similar experience, also after a single dose of antipyrin salicylate, but the connection with the drug was not suspected at the time. Idiosyncrasy could alone explain such results. De Bellard (Gaz. Med. de Caracas, Oct. 15, 1918).

A *skin eruption* is one of the most frequent of these unpleasant results and is, in fact, oftener seen after antipyrin than after either acetanilide or acetphenetidin. It is generally erythematous, and, according to H. C. Wood, "in its most typical form it consists of small, reddish, irregularly circular spots, resembling somewhat those of measles, and arranged in patches separated by sound skin." Urticarial and even bullous and eczematous types of eruption have also been recorded. *Edema*, particularly of the face or extremities, may accompany the eruption, which is also sometimes attended with fever and circulatory disorder. Pigmentation may follow, especially if the eruption has been produced repeatedly.

Of 488 cases of antipyrin poisoning reported by 299 observers in the literature from 1884 to 1907, 10, or about 2 per cent., are reported to have resulted fatally. In a number of instances a single dose of 5 grains (0.32 Gm.) or less has produced alarming symptoms, while a dose of 10 or 15 grains (0.65 to 1 Gm.) has produced serious collapse. Untoward symptoms appeared so promptly in many cases as to lead some observers to believe that the manifestations are largely reflex in character, inasmuch as there appeared to be almost no time allowed for absorption of the drug from the stomach between the time of ingestion and the appearance of the symptoms. This uncertainty of results has undoubtedly been an important factor in bringing about a more conservative use of the drug. In the reported cases of poisoning the

cutaneous symptoms consisted most often of a rash or eruption of varying type, frequently with swelling and severe itching. Generally the symptoms appeared promptly after the ingestion of the drug; in other cases they were delayed, sometimes for several days. They usually came suddenly and lasted only a few hours. In not a few instances their disappearance was followed by desquamation. Edema usually affecting first the face, especially the skin around the eyes, but sometimes becoming quite general, was also observed. Cyanosis was noted in only 2 or 3 cases, and pruritus unaccompanied by a rash in a very few instances. Kebler, Morgan, and Rupp (U. S. Dept. of Agriculture, Bureau of Chemistry, Bull. No. 126, July 3, 1909).

The *mucous membranes* in many instances show similar evidences of irritation or active vascular disturbance. Swelling of the buccal, nasal, and laryngeal mucosæ may occur, and catarrhal inflammation of the conjunctivæ has also been recorded. The respiratory mucous membranes may become so greatly engorged as to render breathing difficult.

Nausea and *vomiting* occasionally result where there is excessive gastric irritability. Burning sensations in the epigastrium and *diarrhea* are also sometimes produced even by moderate doses.

Case of a woman 42 years of age in whom six 7½-grain (0.5 Gm.) doses of antipyrin taken successively within a period of three hours caused persistent vomiting, vertigo, great prostration, and loss of consciousness. Azéma (Toulouse méd., Sept., 1907).

Case of poisoning from 7½ grains (0.5 Gm.) of antipyrin in a woman in childbed. An erythematous rash first appeared. Edema of the lower limbs and diarrhea ensued on the following day. Gilles (Toulouse méd., Sept., 1907).

Sweating as an accompaniment of the action of full doses of the drug has already been referred to. In some cases, especially the tuberculous, it may be so pronounced as to become a source of great discomfort.

Shivering occurs where a marked fall of temperature has been produced by the drug, and is evidence of an attempt on the part of the heat-regulating centers, as the effect of the drug upon them is waning, to increase heat production through stimulation of oxidative processes in the muscles. This is, in reality, an effect for which the antipyrin is only indirectly responsible.

Cyanosis occurs less frequently after antipyrin than after acetanilide. This is doubtless owing to the fact that the former is much less active as a producer of methemoglobin than the latter. When cyanosis does occur, there is frequently dyspnea and cardiac acceleration. After large amounts of these drugs, cyanosis may result from circulatory depression, without any changes in the blood having necessarily occurred.

Collapse, like cyanosis, is less to be feared after antipyrin than after acetanilide, but it is said to occur more frequently with the former than with acetphenetidin. Though witnessed regularly in acute poisoning by massive doses of antipyrin, it has also frequently occurred under moderate doses of the drug, especially, though not exclusively, when used for the purpose of reducing fever. Sudden drops in the temperature are said particularly to invite the occurrence of collapse. The symptoms, of which the most important is cardiac weakness, may be but mild and transitory. In other cases, however,—more prop-

erly to be classed as acute antipyrin poisoning,—progressive circulatory enfeeblement may take place and death ensue. The cause of collapse under moderate doses may refer to some special circulatory weakness—temporary, as in acute infections, or permanent—or to idiosyncrasy, but collapse has also been ascribed directly to the sudden fall of temperature sometimes occurring, on the ground that heat is a stimulant, and that its absence or reduction is, therefore, conducive to depression. Menstruating women are said to be especially liable to collapse (Sollmann).

Ischuria, albuminuria, and hematuria are among the more rarely encountered untoward effects of antipyrin. The relative frequency of their occurrence seems to correspond to the order in which they are here given. Renal disturbances already present may figure as a predisposing factor.

Case of a woman of 29 who, twenty minutes after taking her usual remedy for headache, a 7½-grain (0.5 Gm.) cachet of antipyrin, began to sneeze violently and persistently. Lachrymation, running at the nose, and dryness of the throat were noted, followed by dyspnea and marked precordial distress. The face became suffused, the lower extremities began to itch, and an erythema appeared, extending upward from the limbs, and eventually becoming general, though the face was spared. The respiration resembled the Cheyne-Stokes type, and the pulse was 120, regular. The symptoms disappeared in a few hours after ingestion of hot tea and a hypodermic injection of caffeine, which induced copious diuresis. The itching was relieved with a mentholated paste and starch powder. The case was interesting in that there was shown a sudden intolerance to a dose of the drug habitually taken with impunity. The

intolerance was probably due to impaired renal function, as the patient had noticed on the preceding days that less urine was being passed than usual. Devoir (Bull. de la Soc. Méd. de l'Yonne, xlvii, 1906, p. ix).

Symptoms resembling those of cinchonism, especially *vertigo* and *tininitus aurium*, are, in rare instances, produced.

Temporary *loss of vision* has been recorded several times.

Case of man 33 years old who had been in the habit of taking coal-tar analgesics for several years. Upon taking 130 grains (8.5 Gm.) of antipyrin within a period of forty-eight hours, vision became greatly impaired and two days after was entirely gone. Later it gradually returned. Hotz (Arch. of Ophthal., No. 35, 1906).

A paradoxical *rise in temperature* has been mentioned by Lépine as occasionally following the use of antipyrin.

ACUTE POISONING.

Of the symptoms witnessed when antipyrin is taken in poisonous amount, either in a single large or in repeated smaller doses, lassitude and cyanosis are among the first to appear. Typically the bluish hue is seen first in the face and hands, spreading later to other surfaces. There may be vomiting and abdominal pain. The pulse, at first, perhaps, accelerated, soon shows signs of weakening, and the extremities become cold. Drowsiness appears, the skin may become partially anesthetic, and consciousness is soon after lost. This may be preceded or accompanied by a stage of nervous excitement involving the lower brain-centers and spinal cord, manifested in exaggerated reflex irritability, tremors, or actual epileptiform convulsions. When this disturbance

subsides a pronounced fall in temperature and progressive collapse occur. The pulse becomes infrequent and feeble, the respiration is slow and stertorous—sometimes of Cheyne-Stokes rhythm—and the pupils are dilated and no longer react to light. Death may occur either from respiratory or circulatory failure. In cases that do not end fatally, itching of the skin and an erythematous rash not uncommonly appear during the period of recovery.

The lethal dose of antipyrin cannot be definitely stated, owing to the great variation in its effects in different individuals. In a case of Barr's (cited by Wood), 35 grains (2.25 Gm.) given to a puerperal woman, followed in three hours by half this amount, caused death. Forty-five grains (3 Gm.) had a fatal effect in a patient with cardiac weakness (Butler). In the average case 30 grains (2 Gm.) are required to induce dangerous symptoms, though in a few instances serious poisoning has been caused by doses of 10 grains (0.65 Gm.) or less.

Of 192 physicians questioned on the subject of antipyrin poisoning, 89, or 46.3 per cent., stated that they had observed toxic effects from this drug (as compared with 76 per cent. of 288 physicians having seen instances of acetanilide poisoning, and 21.5 per cent. of 306 physicians having seen instances of acetphenetidin poisoning). These 89 observers reported 105 cases of poisoning by antipyrin, including 5 deaths, *i.e.*, 4.7 per cent. The character of the fatal cases and the doses used were as follows:—

Pneumonia, 10 grains (0.65 Gm.) every two or three hours. Death on third day.

Fever (child), 20 grains (1.3 Gm.). Death in two hours.

Acute rheumatism, antipyrin dis-

pensed instead of "aspirin," quantity not stated. Patient died suddenly.

Headache, 10 grains (0.65 Gm.) followed by 15 grains (1 Gm.) in an hour.

Neuralgia, 5 grains (0.32 Gm.) every three to four hours; 1 dram (4 Gm.) taken in two days.

Kebler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 136, July 3, 1909).

TREATMENT OF ACUTE POISONING.—The patient should be placed in the recumbent posture and the clothes loosened. The stomach may be washed out, or an emetic administered, if it seems likely that some of the drug has not yet been absorbed; in cases with marked circulatory depression, however, the advisability of this measure is doubtful. The chief danger to be apprehended in this condition being circulatory failure, stimulants such as **caffeine** or **hot, strong coffee**, **digitalis** or **digitalin**, **strychnine**, **atropine**, **camphor**, and **aromatic spirits of ammonia** or **ammonium carbonate** are indicated. Dyspnea, if severe, may be relieved by **oxygen inhalations**. **Saline solution** by enteroclysis or hypodermoclysis may be availed of. The application of **external heat**, to compensate for the excessive amount lost, is a valuable measure. **Artificial respiration** is helpful in desperate cases.

CHRONIC POISONING.

Reported instances of chronic disturbances caused by the continual ingestion of antipyrin, similar to those induced by acetanilide, are exceedingly few—so much so that antipyrin would appear to be a much safer drug in this respect than acetanilide and even acetphenetidin. Skin affections; edema, especially facial; digestive disturbances, mental hyperexcitability, and

pronounced tremor are the symptoms which have been most frequently witnessed after the prolonged use of antipyrin. Dauernst observed a case in which the nervous symptoms produced by the drug resembled those of disseminated sclerosis.

In the replies of 400 physicians to a set of questions, 112 instances of acetanilide habit were reported, 7 of antipyrin habit, and 17 of acetphenetidin habit. Ill effects were observed in 85 of the acetanilide cases, 2 of the antipyrin cases, and 7 of the acetphenetidin cases. Kebler, Morgan, and Rupp (U. S. Dept. of Agricul., Bureau of Chemistry, Bull. No. 136, July 3, 1909).

TREATMENT OF CHRONIC POISONING.—For information concerning the management of these cases the reader is referred to the corresponding section under Acetanilide.

THERAPEUTICS.—As **Antipyretic**.—In febrile cases, provided the temperature be very high, the use of coal-tar antipyretics, including antipyrin, is still sometimes recommended, though in recent years the tendency has been to discard these drugs whenever other means to a similar end, especially hydrotherapeutic measures, can be employed. It is only in cases of **hyperpyrexia** (temperature above 105.5° F.) that a drug such as antipyrin may be said to be indicated.

However favorable the high temperature in these cases may be for the destruction of noxæ, a great waste of the nitrogenous body constituents takes place through accelerated catabolism, and this state of affairs leads rapidly to emaciation, diminished alkalinity of the blood, and degeneration of important organs (Sollmann). It becomes necessary,

therefore, to apply simultaneously all effective methods of reducing the temperature at our disposal, including the coal-tar drugs, even though, in cases where the fever is more moderate, these drugs have no advantage over cold baths, except in sparing the patient the inconvenience and exertion which the latter entail. In cases with known or suspected cardiac or renal weakness, however, special caution in dosage is required, or, preferably, total abstention from the use of the drug. In typhoid fever especially are untoward results to be feared and guarded against. Since febrile cases in general are well known to be more susceptible to the unfavorable or dangerous effects of the coal-tar drugs than the afebrile, it is well to administer the antipyrin in small, frequently repeated doses rather than massive single doses. Thus, $7\frac{1}{2}$ grains (0.5 Gm.) may be given at first, and repeated later if the action is inadequate or when it begins to wear off.

The effect of antipyrin on the temperature begins in about half an hour after its ingestion, and continues for a variable number of hours (from two to ten, according to Wood). Pronounced diaphoresis frequently accompanies the action of antipyrin—distinctly greater, on an average, than that observed after acetanilide or acetphenetidin.

In addition to these effects the drug may to a certain extent overcome restlessness and delirium—a fact which formerly caused antipyrin to be used considerably in the febrile affections of children (**pneumonia, typhoid fever, scarlatina**, etc.), irrespective of hyperpyrexia.

[So many deaths occurred when antipyrin was used as an antipyretic that it is

preferable never to use it in febrile infections. Its antipyretic action even at best is but an artificial one, since it is only the surface temperature that is reduced, while the central temperature is raised. This applies also to chronic febrile infections referred to below. C. E. DE M. S.]

In the hectic febrile movements of **pulmonary tuberculosis** antipyrin has been tried, sometimes with asserted satisfactory results. The diaphoretic action is, however, a marked disadvantage. In the long run, the drug proves too depressing, and cannot be recommended in these cases, all the more since a certain degree of tolerance to it may be established upon repeated use, necessitating an increase in dosage for the securing of adequate effects.

In **intermittent fever**, antipyrin has also been used; it exerts no specific action on the causative plasmodium, and is, therefore, in general, immeasurably inferior to quinine. In chronic forms of malaria, however, it has sometimes proven beneficial where quinine failed to act (Antony). In severe malarial cases where it is desired to inject quinine hypodermically, antipyrin has been given in combination with this drug, according to Laveran's formula (quinine hydrochloride, 3; antipyrin, 2; distilled water, 6); the antipyrin increases the solubility of the quinine salt. Santeson found this plan satisfactory.

As Analgesic.—Antipyrin is now of far greater importance as an analgesic than as an antipyretic. Its efficacy in pains of the neuralgic type has brought it into deserved prominence as an advantageous substitute for morphine in these cases. In certain conditions its effect is actually superior to that of opiates. In pain arising from inflammatory dis-

orders, however, its action does not replace that of opium.

In **migraine** and other forms of **neuralgia**, amounts ranging from 5 to 15 grains (0.32 to 1 Gm.), given in successive doses of 5 grains (0.32 Gm.) each, at one-half to one hour intervals, will in most instances give relief. **Sciatic** pains also frequently yield to antipyrin, though with less uniformity than other varieties of neuralgia.

In the "lightning pains" and "gastric crises" of **tabes** antipyrin has been prescribed with variable results. Doses so large as to be more or less unsafe are generally required to produce an impression on these pains.

In **herpes zoster** ("shingles") the drug is often effective.

Antipyrin by rectal injection is recommended by the writer. Montenius has used it in the form of a small rectal injection in **infantile convulsions** and vomiting in doses of from 0.25 to 0.5 Gm. (4 to 8 grains) dissolved in 15 c.c. ($\frac{1}{2}$ ounce) of water. Guyon and Guiard found that given in this way with the addition of a small dose of opium, antipyrin acts as a marked sedative in disorders of the **bladder**, especially in **prostatic disorders**. Mastboom employs antipyrin in the treatment of pelvic **neuralgias**, **dysmenorrhea**, and **coccygodynia**, according to the following formula which he has employed in a large number of these commonplace disorders.

R. Cocaine hydrochloride 0.10 Gm. ($\frac{1}{2}$ gr.).
Antipyrin 10 Gm. ($2\frac{1}{2}$ dr.).
Distilled water. 30 Gm. (1 oz.).

Of this solution 1 teaspoonful is to be administered in the form of an enema. A. Guérin (*Jour. de Méd. de Bordeaux; Med. Rec.*, Jan. 25, 1913).

The value of antipyrin in **chronic rheumatic** or **gouty** pains was empha-

sized by Germain Sée. In **acute rheumatism** the drug was also lauded by the same author as being superior to salicylates in *afebrile* cases. According to Manquat, antipyrin is preferable to salicylates in cases where there are cardiac complications, especially where the organ is in a state of "erethism," as it is less of a depressant to the heart than salicylates (exception is to be made, however, of cases having an idiosyncrasy to antipyrin). He quotes Clément, moreover, as having found antipyrin to hasten the resolution of serous involvements in this affection.

In **influenza**, especially where attended with pains in the back and headache, antipyrin has proven itself a valuable remedy. The greater the asthenia in any given case, however, the more caution should be exercised in its use. Acetphenetidin, the mildest of the coal-tar analgesics in common use, is sometimes recommended in preference to antipyrin.

In **pseudoangina pectoris** antipyrin has been lauded as an analgesic. In true **angina pectoris**, however, granting that antipyrin is a constrictor of the central blood-vessels, the use of the drug would seem to be irrational, though Sée reported having arrested anginal attacks in 4 cases by means of injections of antipyrin and inhalations of pyridine (Manquat).

As Antispasmodic and General Sedative.—In **whooping-cough** antipyrin is used as a sedative with marked benefit in many cases. It probably exerts no advantageous effect on the course of the disease in general, though le Goff has claimed that the duration of the affection is shortened. Its chief service is that of lessening the frequency and sever-

ity of the paroxysms of coughing, seemingly by diminishing the irritability of the superior laryngeal nerve or its receptive center. Dubousquet-Laborderie used antipyrin in 300 cases, with 9 deaths; he gave it in daily doses of 0.2 to 0.3 Gm. (3 to 5 grains) at first, later increased to 1.5 Gm. (23 grains) or more. In very young children it is best given immediately after the paroxysms; in older children, with the meals.

Antipyrin found to be the most serviceable of all drugs in an epidemic of **whooping-cough**. It seldom failed after two or three doses to stop the vomiting after the coughing spells, even in cases where it did not appear to influence the paroxysms themselves. In most instances the frequency of the latter would diminish to one-half or less. The dose usually found efficient was 1 to 3 grains (0.065 to 0.2 Gm.) four to six times daily. By doubling the dose at bedtime, a comparatively quiet night's rest was often obtained. H. N. Fletcher (Practitioner, April, 1907).

Report of cases of **pertussis** in which 15 drops (0.9 c.c.) of a 2 per cent. solution of antipyrin were injected into the larynx, with marked success, by means of a special pipette devised by Yankauer. Fendler (Amer. Jour. of Obstet., June, 1908).

Quinine and *antipyrin* can be depended on to abort or attenuate pertussis, but, as usually given, the dislike of the child to take the medicine leads to inadequate dosage or to its total neglect. This can be obviated by injecting a solution of the drug into the rectum. The writer has 1 Gm. (15 grains) dissolved in 25 Gm. (6 drams) warm water and injected three times a day, for a child over 12, with smaller doses for children younger. No ill effects have ever been noticed on the heart, while, when the injections are commenced early, the disease is frequently aborted. It does not depress the

appetite given in this way, and the therapeutic effect seems to be constant and reliable. Senftleben (Deut. med. Woch., Jan. 14, 1909).

In **chorea** antipyrin is highly recommended by some observers, though in the hands of others it has not yielded any particularly striking results. According to Scribner, the drug is effective in reducing the spasmodic movements and in relieving the muscular and joint pains. Progressive increase in dosage is often necessary in order to keep up the primary beneficial results. It is recommended, however, to give the drug in small, frequently repeated doses, rather than fewer, massive doses, in order that, upon the appearance of untoward effects (cyanosis especially), the sudden and tardy advent of which is one of the unpleasant features of the action of this drug, stoppage of the remedy may lead to a more prompt arrest of its action. For a child of 5 years the proper initial dose would be 2 or 3 grains (0.13 to 0.2 Gm.) every three or four hours. The drug should not be administered too long. Small doses of digitalis may advantageously be combined with it for greater safety (Scribner).

In some cases of **hay fever** antipyrin in full doses has been found useful, though it should not be continued for any length of time.

In **exophthalmic goiter** antipyrin has occasionally proven useful. Cazal employed it to reduce nervousness through sedation of the centers. Hinshelwood reported a case in which it removed Stellwag's symptom (retraction of the upper lid), though Graefe's symptom persisted.

Antipyrin has been employed with indifferent success as a nerve seda-

tive in certain other affections, including epilepsy, bronchial asthma, and seasickness.

In children antipyrin has proven useful as a general sedative in many conditions associated with evidences of excessive irritability of sensory nervous structures. In small doses it seems to be almost uniformly well borne in childhood, and its freedom from hemolytic action and from the tendency which acetanilide and acetphenetidin possess to produce cyanosis is an advantage.

Antipyrin found useful in conditions of nervous irritability, pain, sleeplessness, etc., associated with **teething**. **Nervous instability** leading to vomiting, diarrhea, cough, or even eczema at the eruption of every new tooth or set of teeth is sometimes removed, and the symptoms checked, by antipyrin. This includes those cases of rickets in which **dentition** is associated with nervous symptoms, though, of course, antirachitic treatment is indicated in addition. Dose used, 1 to 2 grains (0.65 to 0.13 Gm.) two or three times daily. The drug proved strikingly effective in 3 children with "night terrors." The true cause, *c.g.*, depressed general health, digestive disorder, rickets, congenital syphilis, or adenoids, must, however, always be sought and removed in these cases. H. N. Fletcher (Practitioner, April, 1907).

In **dysmenorrhea** its use was recommended by E. C. Rothrock and E. E. Montgomery.

For relieving the so-called "**after-pains**" succeeding childbirth antipyrin has been found useful. It has also been used with some benefit for the purpose of quieting a tendency to the development of pains before the full term has been reached.

During **lactation** antipyrin may be given to control or suppress the mammary function.

In **diabetes mellitus** antipyrin brings about a prompt, more or less marked, but merely temporary diminution in the degree of glycosuria, as well as of other symptoms. According to Manquat, cases in which the elimination of sugar does not exceed 80 to 100 Gm. ($2\frac{1}{2}$ to 3 ounces) to the liter of urine can be entirely relieved for a time by a combination of antipyrin with suitable diet; where the glycosuria is more pronounced, improvement may nevertheless be obtained; but in emaciated patients, with glycosuria exceeding 150 Gm. (5 ounces), no results whatever are to be expected. Even in favorable cases, continued benefit from antipyrin can only be obtained by intermitting the administration of the drug from time to time, *c.g.*, giving it for eight or ten days, then stopping it for a week. Digestive disturbances and albuminuria may result upon continued use of the drug. The present tendency is to restrict the use of antipyrin to cases showing particular nervous phenomena, such as undue excitability, restlessness, etc.

The manner in which the coal-tar drugs act in diabetes is not known. According to some, they act as nerve sedatives, controlling the excessive glycogenesis resulting from nervous overactivity.

In **polyuria** of medullary origin, antipyrin is known to be effective. In that of interstitial nephritis, however, it does no good and, in fact, is contra-indicated (Huchard).

Local Uses. — Locally, antipyrin may be employed for its analgesic, antiseptic, and styptic effects. St. Hilaire and Coupard have used it in conditions attended with **pharyngeal** and **laryngeal** irritation, and have demonstrated its useful local anes-

thetic properties. They recommend a solution of 1 part of the drug in $2\frac{1}{2}$ parts of distilled water, employed as a spray. According to the former observer, the complete insensibility produced by this strong solution persists for one to two hours.

The writer lays stress on the value of antipyrin as a **local anesthetic** now often employed as a styptic in hemorrhage. Its astringent action renders it suitable also in painful inflammations, such as **stomatitis**, **gingivitis**, etc. While its action is not as strong as that of cocaine, relief is more lasting and effective, because the process of inflammation is abated. Even in **ulcerative carcinoma** of the **tongue**, antipyrin is very effective in alleviating the **glossitis** complicating these ulcerations. For these local applications by painting, a simple aqueous solution of 1:10 is employed. For mouth-washes or gargles a 1:50 solution is used. The disagreeable taste of antipyrin can be considerably improved by the addition of glycerin. A. F. Plicque (*L'Odontologie; Dental Cosmos*, Jan., 1913).

Under ordinary circumstances, however, a 2 to 4 per cent. spray is sufficient to afford relief in **acute coryza** or pharyngeal irritation. Antipyrin brought in contact with mucous membranes causes considerable smarting and burning, especially if used in 4 per cent. or stronger solutions; it is, therefore, advisable always to precede its use by the application of cocaine.

In **tonsillitis** antipyrin may be used in the form of a gargle. Some care is, of course, necessary as to dosage, and the patient should be instructed not to swallow the solution after gargling.

In **cystitis** with ammoniacal urine Cazeneuve found antipyrin in 4 per cent. solution serviceable. The pain was diminished and the character of the urine improved.

Pruritus is sometimes relieved by antipyrin.

As a local anesthetic in operative procedures involving mucous membranes antipyrin has been used to some extent, but in comparison with the numerous good local anesthetics more recently introduced it presents no advantage.

Clinical experience with antipyrin as a local anesthetic. Employed in 50 per cent. solution as a local application to the mucous membrane of the nose, it brought about a deep anesthesia. However, it was so slow in its action that even when used with adrenalin several applications at intervals of two to three minutes had to be made before insensibility of the membrane resulted.

The writer also reports the use of antipyrin by injection, preceded by the application of quinine and urea hydrochloride and adrenalin to the mucous membrane, for the resection of the turbinate bones, having employed it successfully 23 times without ill effects. A. Ephriam (*Kentucky Med. Jour.*, Nov. 1, 1911).

Hypodermic or intramuscular injections of a 25 to 50 per cent. antipyrin solution have been given in order to secure the analgesic effect directly at the seat of pain in such conditions as **sciatica**, **supraorbital neuralgia**, etc.

Bergquist employed this measure, followed by massage at the point of injection, in 130 cases of **lumbago**, and reported 122 as having been cured. The injections themselves, however, caused very sharp pain lasting half a minute. They have also been known to produce local necrosis and abscess formation (Ricochon and Verneuil).

In the presence of neuritis such injections are believed to be especially injurious.

In **local hemorrhages** antipyrin is valuable as a styptic. It is believed to act by constricting the vessels and inducing retraction of the tissues. The antiseptic property of the drug is also useful under these circumstances, antagonizing the development of bacteria in the clot. In **epistaxis** antipyrin may be applied to the bleeding point in a 10 to 50 per cent. solution by means of a tampon. The first-named strength of solution is generally sufficient for all ordinary purposes. Roswell Park has advised a sterile 5 per cent. solution, used as a spray, on a compress, or as an injection. In addition to epistaxis, the drug has been used with success in **dental, tonsillar, and uterine hemorrhages**.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

ANUS, DISEASES OF. See
RECTUM AND ANUS, DISEASES OF.

APHASIA.—SYNONYMS.—
Aphrasia; alalia.

DEFINITION.—Aphasia is a partial or total loss of the power of expressing one's self in speech or of understanding speech, which is dependent upon cerebral disorder.

VARIETIES.—Two chief divisions of the affection: motor, or emissive or projective, aphasia, and sensory, or receptive or subjective, aphasia are recognized. Each variety includes at least two elementary forms: aphemia and agraphia, as motor subdivisions, and visual aphasia, or word-blindness (alexia), and auditory aphasia, or word-deafness, as subvarieties of sensory aphasia.

The motor aphasia may be complete (aphemia) or there may be only some partial defect in the emissive mechanism of speech (dyslexia, paralexia, articulative ataxia, paraphasia, paralalia). The agraphia may likewise be complete (agraphia) or partial (paragraphia, dysgraphia). Pantomimic speech, so called,—which is an emissive form of speech in gestures, signs, etc.,—may be affected totally (amimia) or partially (paramimia) also. The more elaborate subdivisions of sensory aphasia are based upon qualitative rather than quantitative impairment. In the older literature all forms of sensory aphasia were referred to collectively under the term "amnesic aphasia," which included loss of the pictorial memory of letters and words and of the sounds of letters, words, and music. It included, also, loss of the power of understanding the meaning of figures, written music, and other symbols.

In the more recent literature of the subject the term "amnesic aphasia" has been rather arbitrarily restricted to a loss of the naming rather than the ideational functions of speech-memory. Loss of the ideational faculty is expressed by the term "apraxia" (mind- or soul- blindness). Both sensory and motor aphasia may be divided, as regards the anatomical basis, into the cortical and subcortical varieties. The terms "conceptional" and "conductive" are practically of identical significance with the terms "cortical" and "subcortical."

The writer lays stress upon the necessity for 8 forms of tests, tests for spontaneous speech, for repeated words, reading aloud, spontaneous writing, writing from a copy and writing from dictation, study of comprehension of spoken words, and

study of comprehension of printed words.

In apraxia the simple reflex and expressive movements must be studied as well as the descriptive and other movements, as he enumerates in detail. Laignel-Lavastine (Bull. méd., Mar. 20, 1920).

In a study of the difficulty in finding the proper word in aphasia the writer found that the difficulty is much greater for names of unseen objects than for the visible, and that this must be borne in mind, in addition to other features while in training during convalescence when total aphasia exists. F. Lotmar (Schweizer Archiv f. Neurol. u. Psych., Apr., 1920).

SYMPTOMS. — Motor Aphasia (Aphemia).—In motor aphasia the voluntary act which must be carried out to give expression to thought by the phonetic co-ordination of the muscles of the larynx, tongue, soft palate, and lips is not performed. The patient is seldom unable to produce sound, but he can no longer produce an articulate sound. Although he understands what is said and can think, he is unable to give expression to his thought; it may be possible for him to pronounce letters or even meaningless words,—he may even retain some words,—but these are usually interjections of some kind. In some cases, nouns only or verbs only are forgotten. One language may be forgotten and another remembered. This variety of aphasia is usually encountered in persons who are affected with right hemiplegia. In some, however, who are left-handed, there may be left hemiplegia. In some cases, although speech is impossible, the patient can articulate in singing, especially if certain well-known airs are sung, the words in that case having become intimately connected with the notes.

Our present means of research are unable to determine the exact connection between the Broca localization and the remainder of the cortex. There is evidently a comprehensive and complicated center for speech, or rather an area of excitation, both synchronous and successive excitation, of the foci aggregate. Monakow (Deut. med. Woch., Sept. 23, 1909).

Agraphia.—Agraphia consists in the loss of the memory of the necessary movements to write. In an uncomplicated case the patient is able to speak, hear, or read as usual, but when he tries to write he finds that he can no longer do so, though he is capable of copying letters or designs placed before him. Pure agraphia is uncommon. It is usually associated with some aphemia.

Agraphia can only occur in those persons whose education is sufficient to enable them to write automatically.

Amimia.—Sign-language, as practised by deaf-mutes in gestures and pantomimic speech generally, may be affected by a cerebral lesion. Loss of pantomimic speech is often coexistent with aphemia or agraphia or both. It is rarely or never found alone, although it is quite possible to conceive of its separate existence in one in whom this faculty had been especially cultivated (Mills).

Sensory Aphasia.—Auditory Aphasia.—This variety is more rarely met with than motor aphasia. Both the reception and production of audible speech are deficient, the leading symptoms being, on the receptive side, word-deafness and, on the productive side, word-amnesia and articulative amnesia. Speech and separate words are distinctly heard by the subject, but no meaning is attached to them. Sounds, however,—such as that of an engine-whistle, an alarm-clock, the hour,—are

heard and recognized. Right hemiplegia and a certain amount of word-blindness are frequently present. Certain cases of auditory aphasia hear as if spoken to in a foreign tongue, but they cannot understand what is said, although they endeavor to do so. Other patients understand neither what is said to them nor what they themselves say, but can repeat words after another. They repeat like parrots (echolalia) what is said; but if the center of articulate voice is still partially connected with the sensory centers of audition and the latter are normal, the repetition of the word may suddenly give rise, in their mind, to the idea conveyed by the word.

Instead of articulate speech the phenomena may show themselves in connection with music or numbers. In subcortical word-deafness the patient hears, but does not understand. He can, however, repeat at once whatever he hears, and write it down. While writing or speaking he may understand the words used, but not after the mechanical act is accomplished.

Macleod Yearsley has pointed out that this condition is especially important in connection with the examination of school children. Thus, a child aged 11 is very bright and healthy, except for her defect in hearing for spoken speech, and rather more intelligent than normal children of her age. When spoken to she makes an attempt to repeat the sound, but if she sees the lips she does as she is told, and answers as far as she can rationally. The functional tests, after her education has proceeded somewhat by the oral method of treatment, show practically normal results, and the tympanic membranes are healthy. Yet, she can be more easily taught by the oral method, though her response to questions heard is improving. It is difficult to explain such cases on any hypothesis save that of weakness of the auditory center.

Word-blindness (Alexia).—The patient sees written or printed letters and words and may be able to distinguish one from another, but they no longer have any meaning for him. Word-blindness is rarely total, however, a few words or letters being usually understood; nor is the disorder often found existing alone. In nearly every case there coexists either word-deafness or motor aphasia or some other complication of speech.

Word-blindness is often found in connection with right lateral hemianopsia, or concentric diminution of the field of vision. The patient can no longer read, but can write; as he cannot read what he has written, the letters and lines are sometimes uneven and resemble those written with the eyes shut. In the right hemianopsia found in this connection the written lines always begin on the left side of the page. The visual memory of numbers may be preserved or may also be lost (*cacitas numeralis*). Word-blindness can, therefore, be divided into two categories: In the one, the sense of the letter itself is lost (*cacitas literatis*); as a consequence, persons who generally read slowly, and spell out each word, suffer the total loss of the power of reading. In the other, the accompanying hemianopsia prevents the general physiognomy of a word being rapidly taken in by the patient (*cacitas verbalis*).

The writer reported in 1907 4 cases of congenital word-blindness occurring in the same family. Thomas, in 1905, called attention to the fact that congenital word-blindness might assume a family type, and that an hereditary origin was probable. The 4 cases of the writer support this contention, while the 2 now recorded still further confirm the hereditary tendency, since they occur in the second generation of this same family, and are

the children of the oldest daughter; hence, the nephew and niece of the cases previously reported. James Hinshelwood (*Brit. Med. Jour.*, Mar. 18, 1911).

Subcortical Word-blindness.—In subcortical alexia the patient can read or copy, but he does not understand what he does until the movement of his hand awakens in his mind the sense of word-hearing and of motor articulation through the muscular sense.

In pure verbal blindness the meaning of the words may be lost, but, by following with the eye the form of the letters, the patient finally may spell out the word.

Apraxia.—In apraxia (Kusssmaul) the patient no longer recognizes the use of objects which he sees; a fork to him conveys no meaning of its use. Apraxia may affect other senses besides that of sight,—as, for example, hearing, taste, smell, etc.,—the sound of a bell may no longer convey a meaning or the taste of a dish.

DIAGNOSIS.—In all cases of actual or suspected aphasia the patient should be examined as to his ability:

1. (a) To speak voluntarily; (b) to speak clearly and distinctly, pronouncing properly; (c) to repeat words dictated aloud.
2. (a) To write voluntarily letters, words, numerals, and sentences; (b) to write from dictation; (c) to copy; (d) to understand what he has written.
3. (a) To understand words and sentences spoken; (b) to understand or recognize vocal and instrumental music; (c) to understand the use of objects named.
4. (a) To read words, letters, numerals, and musical symbols if previously familiar with them; (b) to call objects by their names; (c) to recognize the use of objects exhibited; (d) to read and comprehend what is read.
5. (a) To name

and recognize the use of objects felt, tasted, or smelt.

Word-deafness must be distinguished from deafness. If the patient does not suffer from aphemia, it will be at once perceived, from his ability to hear simple meaningless sounds, that he is not simply deaf. When word-deafness exists in combination with aphemia and word-blindness (this latter complication is uncommon) the diagnosis must be made between true word-deafness and apparent deafness with dumbness in a non-hemiplegic, demented subject.

If, however, the symptoms have followed an apoplectic stroke with right hemiplegia, the affection is probably word-deafness due to a cortical lesion.

Word-blindness, if isolated, is easily recognized.

Katz reported 2 cases among public school children in both of which there was said to be alexia. Besides the real inability to read on account of congenital word-blindness, there was a pseudoalexia due to astigmatism and other congenital visual defects in a boy in whom the proper glasses corrected the alleged alexia. Visual defects which give an apparent alexia in children may be due to irregularities in the development of the eye as the result of hereditary syphilis.

Aphasia, or Aphemia.—Aphasia should be diagnosticated from (1) mutism due to melancholia; (2) mutism due to hysteria; (3) the silence observed in hemiplegic patients who speak with difficulty; (4) the silence observed in hemiplegic patients who are suffering from pseudobulbar paralysis of cerebral origin; (5) word-blindness associated with word-deafness. All these present individual characters which must be studied in connection with the general symptomatology of each affection.

Centers in the pons and medulla oblongata preside immediately over

mechanical speech, but are indebted for much of their activity to cortical influence. What is known as sub-cortical motor aphasia seems to be a connecting link between aphasia and anarthria, since it presents the phenomena of both the latter. In every case of complete cortical motor aphasia there is a dysarthric component. To be able to demonstrate the presence of the latter, the writer has devised a system of articulation gymnastics requiring speech co-ordination, with graphical methods for recording, which is not put forward as wholly original, since Goldscheider has done work of a similar character, and many others have occupied themselves with experimental phonetics. Tracings show very clearly the differences between normal articulation and dysarthria. Gutzmann (*Deut. med. Woch.*, Oct. 12-19, 1911).

Agraphia arising from a lesion of the center of writing should be distinguished from (1) the purely motor inability to write due to hemiplegia and (2) the agraphia due to a lesion of the visual center in patients of limited education and who copy visual images; (3) the agraphia due to a lesion of the auditory center, in which the patient writes only what is mentally heard by him, but cannot write from dictation.

The coexistence of word-blindness or of word-deafness with agraphia should suggest that the latter might be due to a lesion of the sensory centers (visual or auditory), especially if the patient did not previously write automatically, for agraphia due to a pure lesion can arise only in cases in which automatic writing has caused the development of a special graphic center.

Infracortical Motor Aphasia.—A pure motor aphasia without word-blindness or word-deafness is likely to be of infracortical origin. Cases, how-

ever, have been reported in which an infracortical lesion has caused aphasia, word-blindness, and word-deafness.

ETIOLOGY.—The various varieties of aphasia occur almost always as a manifestation of cerebral lesion. The most common factor is softening from hemorrhage, embolus, or thrombus; next in frequency are cerebral tumors and, especially, syphilitic lesions (Fournier); traumatisms, and meningoencephalitis.

Aphasia may temporarily occur in the course of many acute febrile infections—of the puerperal state, diabetes, nephritis, and gout—without any evidence of organic lesion. General writers have noted its occurrence in typhoid, especially in children and most frequently in boys; and in acute pneumonia, also, aphasia is met with apart from any other cerebral sign of cranial lesion. Aldrich has recorded a case of otherwise uncomplicated small-pox in a boy aged 7 years. He spoke no word for three months after the fall of temperature.

Among 100 aphasic inmates of the Western Pennsylvania Institution for Feeble-minded, Henninger found 35 were epileptics, 14 also paralytics; 20 were cases of cerebral paralysis, and 44 patients were idiots; 29 of the genetous type and 11 microcephalous, 2 hydrocephalic, 2 mongolian, and 1 cretin. Epileptic dementia from severe and frequent convulsions was credited as the cause of the aphasia in 6 of the epileptics, but in most of these cases Henninger considered both the aphasia and the epilepsy alike due to some developmental defect and advises a careful search for mechanical impediments to speech. If the patients do not then respond to treatment, an unfavorable prognosis should be given. In cases of cerebral paralysis, an attempt should be made to educate the uninjured hemisphere whenever there appears to be any possible chance of improvement.

Agraphia in a case of frontal tumor.

This case was of a somewhat unusual character, because of the presence of agraphia as a comparatively isolated symptom in the early stage of the disease, and, even when to this was

added difficulty in use of words and in obeying more complicated spoken commands, still the agraphia was the distinctive feature. Monakow asserts that "pure agraphia" occurs only as a hysterical phenomenon; its relatively isolated occurrence as a symptom without aphasia or apraxia is very rare. The writer also gives a *résumé* from literature of 8 cases of apraxia in 2 of which the left frontal lobe was involved; in the third case the lesion involved the white matter of the frontal convolutions. C. MacFie Campbell (Review of Neurol. and Psych., June, 1911).

About 80 per cent. of all cases of aphasia seen by the writers could be traced to the use of obstetric forceps during delivery. This is not surprising when one considers the condition of the bony tablets at birth and the amount of pressure frequently exerted upon them. Sometimes the inner tablet is split, a callus is formed upon its inner surface through the escape of osteoblastic cells, and thus a dent remains. Chapman, Morris and Simrell (N. Y. Med. Jour., Aug. 2, 1913).

Aphasia may present itself during enteric fever, small-pox, and puerperal fever. Transient aphasia—following epileptic or hysterical convulsions, migraine, or concussion of the brain—has been occasionally observed, and certain degrees of the affection may be temporarily present and even recurrent in states of profound anemia of the cerebrum and in alcoholism of the chronic type.

The hysterical mutism described by Charcot is, according to Courmont, nothing else than aphasia of transmission (aphemia) uncomplicated by agraphia, or verbal deafness or blindness. A mutism is met with in hysterical subjects which may be termed voluntary, is not due to aphasia, and should be differentiated from the hysterical mutism of Charcot.

Case of motor aphasia as a sequela to scarlet fever. The patient, a boy

aged 6, well nourished, had a chronic discharge from the ears, and an attack of measles three months previous to present illness. By the middle of the second week paraplegia of the left side was noticed, with motor aphasia. The patient seemed to understand words, and retained full power of hearing, but the power of articulate speech and of producing complicated movements in the region of speech muscles was wanting. The tongue could not be protruded well and deviated to the left. The paralysis lasted a few weeks, and the patient gradually regained his power of speech three months after illness. N. Lawrey (Jour. Amer. Med. Assoc., July 17, 1909).

Transient aphasia and paralysis or cerebral crises occur in states of high blood-pressure and in arteriosclerosis. The symptoms vary greatly, but tend to repeat themselves in the attacks. Transient aphasia is one of the most common: inability to talk, consciousness of it, no paralysis, emotional disturbance, and, within a few hours, complete recovery; loss of the power to write and hemianopsia may be present. Sensory disturbances rarely occur alone; paresthesiæ may exist with the aphasia. Motor paralysis is the most common symptom, and may be hemiplegia, or only the face and hand or arm may be involved. The paralysis, rarely complete, has a transient character, which with the recurrences give it a peculiar stamp. The prognosis is largely that of sclerosis. W. Osler (Can. Med. Assoc. Jour., Oct., 1911).

Excluding syphilitic cases, the average age of the author's aphasic patients had reached the seventh decade of life. Cardiac, arterial, or renal changes were frequent. It may be assumed that there is commonly in these cases some degenerative change in the cortex or other tissues of the brain with deficient blood supply, the occurrence of aphasia marking a more definite pathological change in some part of the speech areas of the

cortex. This complication increases the gravity of the prognosis and such cases frequently die of cerebral hemorrhage or softening.

Aphasia may supervene on pre-existing insanity or mental decay, no doubt due to vascular or degenerative changes, which might have led to the same result in the absence of the mental disorder. Again, aphasia may be the first symptom indicative of cerebral and mental decay. In such cases the question arises how far the mental disorder is intimately associated with the aphasic disturbance of speech or is due to widespread vascular and nutritive changes in the brain. The mental disorder does not necessarily amount to certifiable insanity, but may in varying degrees affect such mental processes as perception, memory, emotion, and volition, without much disorder of conduct. In all the writer's cases, except those of Broca's aphasia, there was some disorder of mind, though not always marked failure of intelligence. R. Percy Smith (*Jour. of Mental Sci.*, Jan., 1918).

PATHOLOGY.—Motor Aphasia.

—Pure aphasia of articulation is due to a lesion of the foot of the third left frontal convolution (Broca's convolution). If the lesion affects more than this region, other symptoms are present. If the lesion occupies but a portion of the region, the aphasia may be partial only: for instance, nouns only will be missing. In persons habitually left-handed a lesion of the third right frontal convolution may produce motor aphasia. In persons who are ambidextrous the aphasia is of slighter degree and is more transient. The lesion may be either cortical or subcortical. As a rule, in the subcortical cases the defect is rarely complete.

Marie wrote in 1906 a series of very forcible articles denying any relationship whatever between lesions of the

third left frontal convolution (Broca's) and defects of motor speech. He localizes all speech functions in that region of the brain known as "Wernicke's zone," which includes the posterior part of the insula and of the lenticular nucleus and the posterior part of the first two temporal convolutions and part of the occipital lobe. He denies the existence, indeed, of motor aphasia, substituting the term *anarthria*.

Marie claims that Broca's convolution is not concerned in what is usually called "pure motor aphasia," but that the lesion is situated in a quadrilateral area bounded

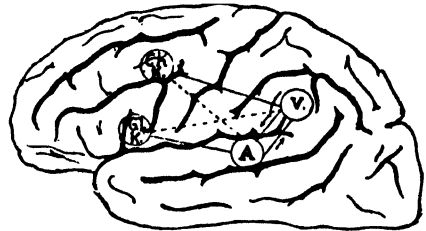


Diagram showing the approximate sites of the four word-centers and their commissures. (*Bastian*.)

in front by a transverse line leading from the anterior end of the insula to the lateral ventricle, internally by the ventricle and the internal edge of the hemisphere, behind by a transverse line leading from the posterior end of the insula to the internal edge of the hemisphere. Marie is inclined to limit the localization still more to a "lenticular zone" situated between the convolutions of the island of Reil and the lenticular nucleus, and in the white matter between the external portions of the lenticular nucleus.

According to Mills and Spiller lesions restricted to the lenticula apparently do not cause sensory symptoms. Motor symptoms probably result from lesions situated in certain parts of the lenticula; speaking generally, the lenticula may be regarded as a motor organ. Anarthric or dysarthric speech disorders result from lesions of some portion of the left lenticula, which probably contains centers

which are concerned with the movements which make speech possible. Destructive lesions of certain portions of the lenticula probably cause a paresis of the limbs or face; the paresis or paralysis caused by such lesions of the lenticula differs from that produced by capsular lesions, the impairment of power being so severe and not being so characteristic in the former as in the latter case; and from that produced by cortical lesions in that it is less likely to be dissociated; although dissociated lenticular paresis may occur.

While the diminution of power which results from a destructive lenticular lesion is permanent, it is usually not intense. Persistent true motor aphasia, as this form of speech disorder is generally understood, is not caused by a lesion restricted to the lenticula, no matter what its size or destructiveness. This insula, cortex, and subcortex play an important part in speech phenomena, one entirely different from that played by the lenticula and the internal capsule; the insula is a part of the cortical motor center for speech, Broca's convolution probably forming with the insula the entire cortical motor center for speech. Motor aphasia may be present without a lesion of the left third frontal convolution.

Necropsy findings in 1 of 3 cases of aphasia previously reported by the writer. Notwithstanding the total destruction of the region supposed to contain the centers for speech, the patient regained the faculty of spontaneous speech, lost for a time. The patient was a woman of 54 with right hemiplegia and contracture, and the mental faculties became more and more clouded to complete dementia, but the speech gradually approached normal. Bernheim (*Revue de méd.*, Feb., 1912).

Clinical histories and necropsy findings in 2 cases in which aphasia was present, substantiated the contentions of Pierre Marie by revealing that a lesion of the left inferior frontal convolution in a right handed individual does not necessarily determine motor aphasia, and that a lesion of the left lenticular region in a right handed individual may in itself suffice to pro-

duce permanent motor aphasia. Archambault (*Jour. of Nerv. and Mental Dis.*, Oct., 1912).

Not one special area alone is involved in the faculty of speech and in the various manifestations of aphasia, but very probably several anatomical elements simultaneously. The multiplicity of lesions ordinarily encountered in cases of aphasia is striking. If Marie did not solve the question of localization of aphasia, he had the great merit of showing the necessity of looking for pathological data in areas other than Broca's and Wernicke's. A. Gordon (*N. Y. Med. Jour.*, Jan. 4, 1913).

Report of autopsy findings of a case of right hemiplegia and aphasia in a woman of 36 years. The hemiplegia improved rapidly, leaving her with defective movements and astereognosis of the hand, diminished tactile sensation, and loss of sense of position of the fingers. The aphasia was at first complete; but eventually the patient became able to speak with some freedom, though she could not string her words together into connected sentences. There was a considerable degree of word blindness and some dysarthria: she could write easy sentences, but was unable to read what she had written, and repetition of words was impossible. After death, which occurred 13 years after the attack, there was complete cortical and subcortical destruction of the lower parts of the second and third left frontal convolutions and the lower third of the ascending frontal convolution. There were diffuse atrophic changes in the insula, the inferior parietal lobule, the angular gyrus and the posterior part of the lenticular nucleus. The writers consider that the case does not support the views put forward by Marie, inasmuch as Broca's convolution was destroyed, with motor aphasia lasting for several months; the association of sensory aphasia with dysarthria was very incomplete; and there was no appreciable defect of intelligence.

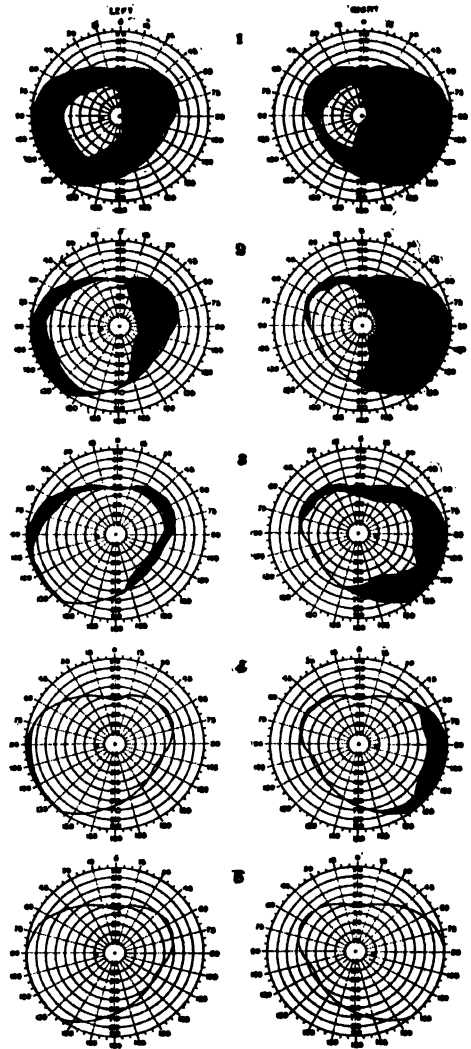
Verger and Desqueyroux (*Jour. de Méd. de Bordeaux*, Mar. 2, 1913).

Specimens illustrating lesions of the left third frontal convolution and of the temporosphenoidal lobe, from cases which had presented respectively motor and sensory aphasia, emphasized the fact that the lesion is seldom so circumscribed as to be confined exclusively to a single center or to a single localization area. W. G. Spiller (*Med. Rec.*, Apr. 11, 1914).

The writer holds that while Broca's convolution is the motor center of speech, it represents only one part of the speech zone, and without a study of the great primary auditory or sensory zone, by means of which the mother tongue is learned, one is likely to make grave mistakes in studying this obscure subject. Language, in its very nature, has a sensory as well as a motor element, and to attempt to separate these two is something like an attempt to separate force from matter, or form from substance. J. H. Lloyd (*N. Y. Med. Jour.*, May 9, 1914).

Agraphia.—True agraphia almost always occurs as a result of a lesion of the foot of the second left frontal convolution or of the subcortical fibers therefrom. Agraphia is generally found, however, associated with some form of motor aphasia, rarely existing alone.

Sensory Aphasia.—Cortical word-deafness is usually caused by a lesion of the middle or posterior portion of the first and second left temporal convolution, chiefly the first. Auditory speech is not, however, so exclusively a left brain function as is motor speech; hence the fact of incomplete and more transient types of speech-defect from unilateral lesions of this region. Lesions affecting the subcortical white fibers from this area give rise to the subcortical type of word-deafness.



Series of perimeter charts in a case of complete agraphia and almost complete word-blindness, with right-sided bilateral temporal hemianopia. (The black area represents the blind parts of the fields.) Chart 1 represents the fields of vision on Nov. 17th. Chart 2 represents the fields of vision on Nov. 24th. Chart 3 represents the fields of vision on Dec. 1st. Chart 4 represents the fields of vision on Dec. 8th. Chart 5 represents the fields of vision on Dec. 15th. (*Byrom Bramwell.*)

Cortical word-blindness is caused by a lesion of the posteroinferior portion of the second left parietal convolution (angulo-occipital region).

Lesions affecting the optic radiations of Gratiolet cause the subcortical variety of alexia. Interruptions of relations through commissural fibers with any of the associated speech-areas will, of course, result in one of the mixed forms of aphasia or in subcortical alexia.

PROGNOSIS.—Functional aphasia associated with hysteria, migraine, epilepsy, fugitive edematous, or toxic states or from intracranial pressure (temporary) or shock, usually disappears promptly; aphasia from syphilitic thrombosis or endarteritis obliterans is also readily responsive to specific treatment. The prognosis is always better in young children than in those of adult life, as much may be accomplished by vicarious or compensatory education of the right brain.

Word-deafness may continue permanently, but it frequently improves through the co-operation of other sensory centers, and especially the visual center. The patient, noting the movements of the lips in those who are speaking to him, recalls motor images which articulation of the same words would require in him.

Word-blindness does not improve in some cases; in others a painstaking and early re-education may be carried out, by which new images may be created in the visual memory by the help of the motor and auditory memories.

Aphasia proper, or aphemia, occasionally remains the same from the beginning to the end, no improvement being visible; usually, however, words return very gradually. Recovery in such cases is never complete.

Some cases recover almost immedi-

ately. This almost always occurs in cases of complete aphasia, and would seem to be of dynamic origin, like the mutism of hysteria or of terrified persons.

Agraphia is in some cases recovered from in the sense that the patient learns to write with the left hand. The writing does not resemble that performed with the right hand, and in some cases it is written from right to left, as in mirror-writing.

Supracortical motor aphasia is less serious than cortical motor aphasia, because the intelligence is less affected, the center of language itself being intact and only the path of communication being interrupted.

Recovery occurs more frequently than in cortical motor aphasia.

TREATMENT.—When there is no paralysis present, mental overwork is a frequent cause of aphasia. Prolonged rest alone secures relief. Any disorder, concomitant or causative, that may be present should receive careful attention. At the same time the patient should be taught to overcome the aphasic symptom; considerable patience is usually required. When the aphasia is associated with right-sided paralysis or convulsions, the treatment of the latter condition by alteratives, **potassium iodide**, or **mercury**, if a syphilitic taint be present, sometimes brings about rapid recovery.

A graphic center should be made to develop in the right side of the brain by practising writing with the left hand. To secure the end in view, it is not sufficient to be able to write legibly with the left hand, each letter being formed by a distinct and sustained effort, the will consciously guiding every movement of the pen or pencil. The required development of the right graphic center is not attained until by practice the move-

ments of the left hand in writing have become instinctive, as those of the right hand are. When this is the case, there is good reason to believe that no lesion of the left side of the brain would deprive the patient of the power to write. And it is far from impossible that the power of speech would also be retained, because of the close functional connection between the speech center and the graphic center. But if only the faculty of writing were preserved, the importance of that to the patient would be immeasurable. F. C. Coley (Practitioner, Aug., 1909).

Case of Déjerine's aphasia, pure motor or Marie's anarthria. The patient was a machinist, 48 years old, who suddenly developed paralysis of the entire right side of the body, with loss of the power of speech. Ability to read and to write both from dictation and from copy, however, remained. A positive Wassermann reaction being obtained, **salvarsan** was introduced into a vein and active mercurial treatment was instituted. Improvement in the symptoms speedily took place and articulate and intelligent speech gradually returned. F. X. Dercum (Med. Rec., Jan. 10, 1914).

Praise of the **psychophysiological method** of speech re-education as an alternative to that which attempts to reteach the motor acts of articulation. The writers' method aims to restore the memory of sounds and the association between visual and auditory (word) impressions, beginning with individual syllables—some of which the patient can still articulate—and later building up polysyllabic words. The method is useful also where the usual method is inapplicable because of weakened intellect and attention. Froment and Monod (Lyon méd., Feb. 15, 1914).

Injury to the skull, especially when there is depression of the inner plate, tumors, cerebral hemorrhage, and other conditions capable of inducing cerebral pressure, requires appropriate surgical procedures.

Case of motor aphasia from subdural hematoma cured by **trephining** added to the 6 successful operations on record. The bullet which caused the hematoma did no further damage, while the compression of the brain substance left the latter quite intact. There were compressed the third frontal convolution (left side) and part of the central convolution, so that there was complete failure of the cortical functions pertaining to this locality. The functions returned completely as soon as the pressure was removed. Borchers (Münch. med. Woch., Dec. 12, 1911).

Traumatic sensory aphasia, the writer states, is often due to subdural hemorrhage pressing on the cortical sensory speech centers. It affects the visual more than the auditory speech center. If treated expectantly, recovery is generally incomplete, and there is a risk of epileptiform convulsions developing later. Treatment by **trephining and removal of the clot** is the best course. Cope (Brit. Jour. of Surg., Apr., 1914).

Case in which, without disturbance of consciousness, there were complete motor aphasia and ecchymosis in the region of the left eyeball, the ophthalmoscope showing changes in both discs, slightly more marked on the left side. A radiogram showed a small linear fracture of the skull on the side opposite to the apparent brain injury.

The skull was opened over the motor area by fashioning an omega-shaped scalp flap. When the dura mater was opened 2 ounces of thick semi-fluid blood escaped. A partially coagulated layer of blood was removed from the under surface of the dura corresponding to the speech center. Blood continued to ooze from the base of the skull. The area was lightly packed with gauze, which was removed at the end of 48 hours. Speech gradually returned to normal in about 7 days. H. A. Haubold (Surg., Gynec., and Obstet., xix, 669, 1914).

WM. BROADDUS PRITCHARD,
New York.

APIOL is obtained from the volatile oil of parsley. At low temperatures apiol is a stearopten or camphoraceous solid made up of needle-like crystals which, at higher temperatures, resolves itself into a yellow or straw-colored liquid. It has a slightly acid reaction and is soluble in alcohol, ether, and chloroform. Most of the apiol of commerce is nothing but an oil of parsley. It may be prepared in various ways, but the methods of manufacturers as published are usually obscure. Green apiol is the oil of parsley loaded with chlorophyll and vegetable fats.

The product of this class most used in therapeutics at the present time is the French *apioline*, "made by exhausting the seeds of *Apium petroselinum* with light petroleum, distilling, washing with alcohol, and treating the washings with caustic soda, which yields the pure apioline on distillation." It is a reddish liquid.

DOSE.—Owing to its unpleasant odor and acrid taste, apiol is best administered in gelatin capsules or perles, each holding from 3 to 5 minims (0.2 to 0.3 c.c.). Two to 4 capsules may be taken daily, preferably night and morning, beginning two or three days before the expected menstrual flow. Apioline is available in 20-cg. (4-minim) capsules; 2 or 3 may be given daily at intervals of from three to six hours to relieve pain or bring on the menstrual flow.

PHYSIOLOGICAL ACTION.—Apiol is thought mainly to act upon the vascular system, causing congestion, and at the same time on the muscular tissue of the uterus. This view is based upon its action as an emmenagogue and by its effects upon the menstrual flow; yet, it is also a regulator of uterine function. It causes, in large doses, cerebral excitement similar to that caused by coffee, with tinnitus, vertigo, and violent headache. Apiol provokes toxic phenomena when used as an abortifacient, i.e., in excessive or very large doses.

Case of poisoning in a woman aged 28, pregnant two and a half months, who took 10 capsules of apiol with the intention of producing abortion. A similar dose was taken in the morning, and, as no result followed, 10 more on the evening of the following day; thus

6 Gm. were taken within forty-eight hours. No symptoms were produced till soon after the third dose, when she began to suffer from severe vertigo which compelled her to lie down, which was soon followed by nausea and vomiting which continued all night. In the morning she observed that her face was red and swollen, the vertigo and vomiting persisted, and were accompanied by diarrhea. At the same time a generalized eruption appeared, for which the writer was summoned, on the third day of the illness. He found an extensive urticarial eruption covering the face, neck, and anterior surface of the chest and abdomen. It was also present on the inner and anterior surfaces of the thighs, legs, and arms, but the extensor area of the limbs was but slightly affected. The face was red and swollen, and the surfaces affected were very itchy. There was slight jaundice, and the liver was large and tender. The urine was scanty and high colored, but without the presence of albumin. The vulva was the seat of considerable edema, but absolutely no action was observed on the uterus and the progress of the pregnancy was unaffected. Under milk diet and a simple diuretic all the symptoms gradually disappeared in the course of a few days. Glatard (The Medical Review; Anti-septic, May, 1911).

THERAPEUTICS.—According to Griffith and Cerna, apiol (apioline) may be regarded as the best emmenagogue at present known. It is indicated in **amenorrhea** due to anemia from whatever cause. W. A. Newman Dorland believes, however, that, in order to insure the best results, it should be combined with some preparation of iron; he also suggests that iron be given uninterruptedly until a few days before the expected appearance of the menses. Then, continuing the iron, apiol may be prescribed in 5-minim (0.3 c.c.) doses, two or three times a day, until the appearance of the menstrual discharge. Apioline is also helpful in **congestive dysmenorrhea** unless this be due to mechanical obstruction; relieving the pain and increasing the flow of this is insufficient. S.

APOCYNUM is the dried root of *Apocynum cannabinum* Linné, also known as American hemp, Indian hemp, dogbane, and Canadian hemp. The plant is native to North America, grows to a height of 6 feet at most, and produces light-greenish flowers. The part used, the root, occurs in commerce in brownish, bark-covered pieces varying from $\frac{1}{8}$ to $\frac{1}{3}$ inch in diameter. It contains, besides tannic acid, gallic acid, and gum resin, two principles known as *apocynin*, a resinous glucosid which readily dissolves in alcohol and ether, but hardly at all in water, and is very toxic, and *apocynin*, a crystalline glucosid which dissolves readily in water, and which, though less active than the former, is analogous to digitalin (Pouchet). Two other active principles, *cynotoxin* and *apocyamarin*, have recently been isolated by Finne-more.

PREPARATIONS AND DOSE.—

The only official preparation is the fluidextract, *fluidextractum apocyni*, prepared from the powdered root. The dose is 5 minims (0.3 c.c.) when the cardiorenal therapeutic action of the drug is to be utilized and 15 minims (0.9 c.c.) to produce emesis. It should not, however, be used for the latter purpose if other emetics are available, since such doses tend to produce gastrointestinal irritation and catharsis. An extract of *Apocynum androse-mifolium*, a wholly inert drug, is sometimes substituted. Hence the need of obtaining it only from an absolutely reliable pharmacist.

Cumarin, a new glucosid of *apocynum cannabinum* was tested by the writer, on animals. He concluded that it is an active cardiac tonic similar in action to drugs of the digitalis

group. V. D. Zelensky (Roussky Vrach, Jan. 25, 1914).

The writer tried cumarin in 30 cases. Its use intravenously in doses of 0.0005 Gm. ($\frac{1}{20}$ grain) to 0.001 Gm. ($\frac{1}{40}$ grain) every second day until about 0.0065 Gm. ($\frac{1}{10}$ grain) had a good effect on the heart and diuresis, but it cannot replace digitalis, although occasionally efficacious where digitalis has failed. It is not followed by untoward symptoms, has no cumulative action, and does not disturb sleep. M. R. Bonsman (Deut. med. Woch., Jan. 1, 1914).

PHYSIOLOGICAL ACTION.—

As emphasized by A. A. Woodhull many years ago, the powerful emetic and cathartic effects which the dispensatory—and various textbooks, we may add—attribute to the root of apocynum result from its unintelligent use, the characteristic effects of the drug, when employed in appropriate doses, being those of a diuretic and cardiovascular stimulant. Hence its frequent classification in the digitalis group.

As a *diuretic*, apocynum earned from Dr. Rush early last century the title of “vegetable trocar” owing to its activity. According to Woodhull, in fact, it seems to have no exact equivalent either in thoroughness or in promptness of action. Under its use Dabney noted that 1 to 2 gallons of urine were passed daily. This action has been attributed to the fact that apocynum increases the contractile power of the cardiac and vascular muscles in therapeutic doses, even the renal vessels being contracted, and thus enhances the excretory activity of the renal filter. Sokoloff, H. C. Wood, Jr., and others found that if a small quantity of apocynum is injected into the vein of a dog a marked slowing of the pulse

occurs, usually accompanied by a very considerable rise of blood-pressure. This action is soon followed by free diuresis. Rose Bradford found that apocynum did not irritate the renal epithelium.

Its action as a *cardiovascular stimulant* is uniformly compared to that of digitalis, even to the possession of its defects: the production of nausea and gastric irritation. It is believed to stimulate the heart muscle and the vessels directly, the view that the cardiovascular phenomena are due exclusively to excitation of the bulbar centers having been found invalid in view of the fact that division of the spinal cord failed to prevent the physiological effects of the drug. Under the influence of the remedy there soon occurs slowing and increased force of the pulse. It tends also to control arrhythmia and to augment the respiratory amplitude.

The vasoconstrictor action of apocynum is considerably more powerful than that of strophanthin; its action on the heart is slightly weaker than that of the latter. On the other hand, it is excreted or destroyed with comparative rapidity, and there is experimental basis for the statement that it is not cumulative in its action. The question whether it is excreted or destroyed within the body remains open for the present. It is thought that the employment of the pure active principle should eliminate the drawbacks which have hitherto restricted the use of this drug, for these are probably due to the presence of other constituents of an irritant nature in the crude extracts. The rapidity with which cynotoxin acts enjoins caution with respect to subcutaneous dosage. Dale and Laidlaw (*Post-Graduate*, Dec., 1910).

In small doses, 1 to 2 drops of the tincture every hour, apocynum slows the heart when its action is too rapid

and increases its force or contractile power, thus resembling digitalis; but it does not have the vasoconstricting and cumulative action of the latter. Large doses, 20 drops repeated, cause vomiting and catharsis. In heart disease it tends to counteract atony of the vascular muscles. A. J. Crance (*N. E. M. A. Quarterly*, Dec., 1911).

Cumarin was found by the writer to be a rapidly acting cardiac stimulant, best given intravenously. It is a true diuretic with a selective action on the renal cells. A. Soldano (*Semana Medica*, June 10, 1915).

POISONING.—The drawbacks of this drug, which, though valuable, is but little used, are in reality due to the injudicious doses often administered. Any dose above 5 minims (0.3 c.c.) tends to produce violent nausea, vomiting, and intestinal disturbances. Sokoloff found experimentally that a toxic dose first produced a pronounced rise of the blood-pressure, and that this was followed by a paralyzing effect on the vasomotor center, the blood-pressure gradually falling to zero. In mammals the heart is stopped in systole, according to Rose Bradford, though a massive dose may stop it in diastole. In man, poisoning tends to be prevented by the emetic action of an overdose.

The *treatment* of apocynum poisoning, were such met, would be similar to that for digitalis, viz., **evacuation of the stomach**, and vasodilators, such as **veratrum viride**, the inhalation of **amyl nitrite**, **nitroglycerin** hypodermically, and the use of **saline solution** at 105° F. intravenously to dilute the blood and favor the passage of plasma into the lymphatic channels.

THERAPEUTICS.—The marked activity of apocynum as a diuretic

renders it valuable in the treatment of **dropsy**, whatever be its cause. The fact that it does not irritate the renal epithelium, notwithstanding its prompt and efficient action and the fact that, unlike digitalis, it is not cumulative, makes it possible to use repeated small doses of apocynum for the purpose of securing eliminative effects superior to those obtained with the trocar. Not only is the operative procedure avoided, but the fluid eliminated is not pure blood-serum, as is the case with the trocar, but true products of excretion eliminated through the physiological intervention of the renal filter. Again, apocynum, even in small doses,—5 minims (0.3 c.c.) or less of the fluid-extract, repeated as needed, three or four times daily,—also enhances intestinal activity for the elimination of fluids—a feature which tends to increase its efficacy in the treatment of **hepatic cirrhosis**, and in **Bright's disease** where this derivative action is desirable. In the edema of **heart lesions**, especially those attended with defective compensation, the drug is of great value owing to its digitalis-like action on the heart muscle.

Apocynum has not taken the rank it deserves in **Bright's disease**. This is because inferior preparations are frequently dispensed. The writer has used the fluidextract in capsules, thus avoiding the nausea so frequently attending the administration of the drug. In a case of mitral regurgitation with inflammation of the kidneys, which had been treated in the usual way by cardiac tonics, baths, and uva ursi, the patient's urine had fallen to 6 ounces in twenty-four hours. The fluidextract of apocynum cannabinum was begun in 8-drop (0.5 c.c.) doses every four hours. Within the next twenty-four hours the urine had increased to 132 fluid-

ounces, and for a week the amount varied from 130 to 160 ounces. The edema disappeared, and the average pulse rate fell from 116 to 92, and its quality was improved. Under the use of the drug the distressing dyspnea disappeared. No permanent benefit was to be expected in a case as severe as this, but the symptomatic improvement was very marked and the comfort of the patient enhanced. R. R. Paine (St. Louis Courier of Medicine, Jan., 1903).

The cardiac disorders in which its efficiency has been found greatest include in particular **mitral** and **aortic insufficiency** with disturbed compensation. The cardiac impulse becomes stronger, the pulse fuller, more regular, and slower. The blood-pressure rising, the dyspnea and cyanosis, if any be present, disappear.

Series of personal cases of **chronic cardiac insufficiency** in which digitalis had failed and apocynum yielded benefit. The action is similar to that of digitalis, though not so durable; when digitalis is contraindicated or has ceased to improve, apocynum may prove advantageous. Fehsenfeld (Münch. med. Woch., Jan. 17, 1911).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

APOMORPHINE.—Apomorphine is an alkaloid obtained by the action of HCl or some other acid or dehydrating agent on morphine, causing each molecule of the latter to lose a molecule of water. A white powder soluble in hot and cold water is formed, a watery solution of which, though colorless at first, soon turns black.

The salt generally employed is the hydrochloride (*apomorphinae hydrochloridum*), made by adding a small quantity of hydrochloric acid to a solution of apomorphine.

PROPERTIES.—This salt occurs in small, grayish-white, acicular crystals, which are odorless and slightly bitter and become green on exposure to light and air. Although Cushny (1910) states that this change of color does not seem to impair the properties of apomorphine perceptibly, in practice a fresh solution of the hydrochloride should always be employed. For hypodermic use reliable tablets extemporaneously dissolved are still better. The hydrochloride is soluble in about 40 parts of water or alcohol. It should be kept in dark amber-colored bottles to avoid the decomposing action of light.

DOSE.—The dose for adults ranges from $\frac{1}{30}$ to $\frac{1}{8}$ grain (0.0022 to 0.008 Gm.); $\frac{1}{10}$ grain (0.0065 Gm.) hypodermically suffices to produce emesis. Great care must be observed in using apomorphine in feeble persons. Death has been caused by $\frac{1}{15}$ grain (0.004 Gm.) under such circumstances. In the case of a drunkard reported by Westby, $\frac{1}{10}$ grain (0.0065 Gm.) of apomorphine, hypodermically administered, followed in five minutes by $\frac{1}{40}$ grain (0.0016 Gm.) more, caused collapse, unconsciousness, cold surface, and absence of pulse at the wrist. For a child of 18 months, $\frac{1}{100}$ grain (0.00065 Gm.) may be used; at 2 years $\frac{1}{80}$ grain (0.0008 Gm.); at 3 years $\frac{1}{70}$ grain (0.0009 Gm.); at 5 years $\frac{1}{60}$ grain (0.0011 Gm.), and at 8 years $\frac{1}{50}$ grain (0.0013 Gm.).

One-fifth grain (0.013 Gm.) should not be exceeded in any strong adult case when given hypodermically, and $\frac{1}{8}$ grain (0.008 Gm.) when administered by the mouth.

MODES OF ADMINISTRATION.—When used as an emetic, apomorphine is given hypodermically in 1 per cent. solution; where employed for

its expectorant properties, it is administered *per os* in small doses, such as $\frac{1}{80}$ grain (0.0022 Gm.).

The drug acts with more vigor in some individuals than in others. Its effects, therefore, should be closely watched. As stated by Murrell, apomorphine, when administered on an empty stomach, produces vomiting much more readily than when administered after a meal. The rate of absorption has much to do with the entire effect. When given hypodermically, the drug is absorbed at once; when given on an empty stomach, it is absorbed more rapidly than when mixed with food.

INCOMPATIBILITIES.—Apomorphine hydrochloride is incompatible with alkalis, tannic acid, ferric chloride, potassium iodide, and silver nitrate.

CONTRAINDICATIONS.—As an emetic, apomorphine is contraindicated, in common with other agents of this class, in cases with pronounced cardiac or vascular weakness, *c.g.*, in the presence of advanced degenerative changes in the heart or of aneurism or atheroma, the rise of blood-pressure induced by vomiting being attended with danger to the integrity of the circulatory organs. Similarly, in cases of poisoning by caustics the use of apomorphine is inadvisable, for obvious reasons. In all conditions of marked general weakness, *c.g.*, in the late stage of poisoning by various drugs, especially narcotics and depressants, the muscular exertion attending the act of vomiting may induce collapse. In all stages of morphine or opium poisoning apomorphine is contraindicated because of the comparatively close relationship existing between it and morphine and the consequent tendency it manifests to add to the general depression caused by the narcotic. Hernia, advanced pregnancy,

pulmonary tuberculosis, and gastric ulcer also contraindicate the use of apomorphine as an emetic.

The consensus of opinion at the present time is that apomorphine is too depressing for children when given in sufficient doses to produce emesis, though valuable in them in spasmodic disorders, *i.e.*, when it can be administered in very small doses.

The doses usually recommended in textbooks are too large. The writer's dose for an adult is $\frac{1}{20}$ grain (0.003 Gm.). This will usually produce the emetic and relaxing result desired, and if it does not it can be repeated. A dose of $\frac{1}{15}$ grain (0.004 Gm.) should be the maximum, and given then only in desperate cases of poisoning. The writer witnessed toxic effects from $\frac{1}{10}$ and $\frac{1}{15}$ gram. The drug should be used only as a last resort in children. F. K. Boland (Atlanta Jour. Rec. of Med., Aug., 1908).

In dogs the evidence in favor of the existence of a central controlling mechanism for the act of vomiting is conclusive; apomorphine acts solely by direct stimulation of this mechanism probably also in man. There is no valid evidence in favor of a local reflex action of this drug.

After intravenous and intramuscular administration no apomorphine was found in the vomitus. This was proven by an ingenious method. A large dog was given the drug several times intravenously, each dose sufficient to produce emesis. The vomitus was collected, evaporated to a small bulk and injected into a much smaller dog with no signs of vomiting; suitable doses of apomorphine had produced emesis immediately preceding and following the injection of the vomitus. After a single large intramuscular injection no apomorphine was found in the vomitus by a similar test. Finally, apomorphine can produce all the symptoms of vomiting (excepting of course the actual expulsion of the gastric

contents) without the presence of a gastrointestinal tract. This was proven by excising the stomach and intestines without development of shock and in such animals the salivary and muscular phenomena "proceed exactly as in the normal animal, so that we can say unhesitatingly that no one who might see a normal dog and an eviscerated one vomit could distinguish the normal from the eviscerated animal so far as the vomiting act is concerned." They have also shown, by the same method, that the emetic action of the digitalis substances is central; this experiment has been confirmed in the laboratory. Eggleston and Hatcher (Jour. of Pharmacol. and Exper. Therap., May, 1912).

PHYSIOLOGICAL ACTION. —

The administration of $\frac{1}{10}$ grain (0.0065 Gm.) hypodermically is followed in scarcely one-half minute by fullness of the head; the pulse is quickened and increased in volume; the pupils slowly dilate; the face is flushed. Perspiration soon appears; the respiration and heartbeats become more frequent; there is more or less depression and muscular weakness, and before two minutes elapse emesis is produced, which may recur three or four times within fifteen or twenty minutes. Then comes the reaction, a general relaxation, lasting about an hour. The eyes are sunken, the pupils are widely dilated, and the face is pallid and drawn. Yawning inaugurates the period of recovery; sleep follows, and, upon awakening, all the effects have passed away.

Series of experiments on derivatives of apomorphine. The most marked physiological actions of apomorphine are two: a paralyzing action exerted on the motor portion of the cord and on the muscles, and an excitation of the vomiting center in the brain, resulting in nausea. In their recent experiments the writers were surprised to discover that it had almost none of the toxic

action which Harnack had previously found, although its action on the vomiting center was the same. Frogs could be killed only by enormous doses or by immersion in solutions of apomorphine. These differences cannot be explained by the presence of impurities in the earlier preparations. There may exist some isomeric forms of apomorphine. Harnack and Hildebrandt (*Archiv f. exper. Pathol. u. Pharmacol.*, Bd. lxi, Hft. 4, 1909).

Salivation and an increase in the nasal and bronchial secretions, lachrymation, and diaphoresis are obtained with small doses of apomorphine, such as $\frac{1}{30}$ to $\frac{1}{25}$ grain (0.0022 to 0.0027 Gm.). Vomiting produced by larger doses is believed to be due to direct stimulation of the bulbar vomiting center. This is shown by the fact that vomiting occurs at once when a solution of apomorphine is applied to the medulla, and also by the relative promptness with which this symptom occurs when the drug is so administered as to cause it to reach the medulla promptly, *i.e.*, by hypodermic injection, as compared to its action when given by the mouth. Ligation of the stomach vessels prevents the emetic action of apomorphine given by the mouth, but does not interfere with its action when introduced into the general circulation.

Experimental administration to animals such as the rabbit, guinea-pig, and other herbivora throws little light upon the physiological action of apomorphine in man, the symptoms produced being totally different—great restlessness and excitability—owing to the inability of these animals to vomit. In dogs the drug causes circus movements, the animals running in a circle; after large doses, there follow tetanic convulsions, and death ensues from respiratory arrest, the heart continuing to beat a brief period thereafter.

Apomorphine differs from morphine in having only a relatively feeble depressant effect on the brain-centers. Neither is it excreted into the gastrointestinal tract, as is the case with morphine. It is probably decomposed in the blood and tissues.

Apomorphine introduced into the organism by hypodermic injection is not found in the material vomited immediately after the injection, nor in the liquid obtained by lavage of the stomach performed from one-half to six hours after the administration of the drug. This indicates that the emetic action of apomorphine resulting from stimulation of the spinal centers is not re-enforced by a local action upon the wall and ganglia of the stomach. Since the apomorphine after absorption is not found as such in the gastrointestinal canal, nor in the urine, it must undergo certain structural modifications within the organism. A. Valenti (*Arch. ital. de biologie*, Sept. 10, 1903).

APOMORPHINE POISONING.

In the human being toxic doses of apomorphine produce unconsciousness, failing circulation and respiration, all accompanied by profound depression and marked weakness, which may pass into alarming collapse. Delirium and convulsions are sometimes observed.

A dose of apomorphine administered subcutaneously caused in the writer severe vomiting, associated during the final act with intense muscular relaxation, such that he had to lie for about half an hour unable to lift a finger or summon aid. Harnack (*Münch. med. Woch.*, Sept. 8, 1908).

TREATMENT OF APOMORPHINE POISONING. — The most effective agent to counteract this condition is **strychnine**, but it should be supplemented by the more diffusible stimulants, as **ammonia**, **whisky**, **coffee**, etc., together with **external heat**.

THERAPEUTICS.—The pronounced value of apomorphine as an emetic is based mainly upon the facts that the average period of time elapsing before the occurrence of emesis is much shorter than that preceding the effect of other emetics, and that its action occurs best after hypodermic administration, thus permitting its employment even when the patient cannot swallow. For good results, it is essential that a pure specimen of the drug be available.

Apomorphine is mainly used, though less than formerly, in the treatment of **acute poisoning** by various drugs or other toxics—gastric lavage, however, being always preferable—when there is any likelihood that some of the poison is still present in the stomach. Occasionally it may be necessary to administer $\frac{1}{10}$ grain (0.0065 Gm.) every ten minutes until some effect is obtained, or exhibit $\frac{1}{4}$ grain (0.016 Gm.) at a single injection. In feeble persons and in children, however, great caution must be exercised. In poisoning due to narcotics or to depressants, such as aconite, veratrum, corrosive sublimate, arsenic, etc., apomorphine not only fails at times to produce emesis, but the added depression its use entails is fraught with considerable danger.

When given by mouth the effects of apomorphine differ widely from those obtained by its hypodermic use. Hypodermically it is a most valuable centric emetic in doses of from $\frac{1}{20}$ to $\frac{1}{60}$ grain (0.003 to 0.001 Gm.), acting quickly and gently. The possibility of depressing effects should be borne in mind when it is given to children, and strychnine should be combined with it. By mouth it has little emetic effect, but acts as an efficient expectorant in doses of $\frac{1}{8}$ grain (0.008 Gm.) every two hours. It does not increase the effect of other narcotics.

It should not be used when there is abundant expectoration. Crystalline apomorphine is to be specified, since the amorphous form is uncertain in its effects. E. L. Fisk (Med. Rec., Sept. 28, 1907).

In **strychnine poisoning** apomorphine has been reported effective as a sedative. Thus, Horsley witnessed a case in which apomorphine, in doses of $\frac{1}{15}$ to $\frac{1}{10}$ grain (0.004 to 0.0065 Gm.) subcutaneously injected, completely subdued the convulsions, and eventually successfully antagonized the excitant alkaloid.

Apomorphine emesis is sometimes helpful when a **foreign body** has lodged in the **esophagus** or in the **pharynx**, the act of vomiting being the expelling agent.

Apomorphine hydrochloride has also been recommended in **cerebral congestion** when it is desirable to empty the stomach quickly. But it should rather be avoided in aged subjects suffering from this condition, owing to the violent rise of blood-pressure which the act of vomiting provokes. Gastric lavage is preferable in such subjects.

It acts as an expectorant and sedative in doses ranging from $\frac{1}{80}$ to $\frac{1}{20}$ grain (0.0008 to 0.0032 Gm.). As such it affords great relief in cases of **bronchitis**, **tracheitis**, and **catarrhal pneumonia**. It has been used advantageously by Arnstein in **laryngeal diphtheria** when the swelling and softening of the false membrane after antitoxin injections cause signs of suffocation. A hypodermic dose of $\frac{1}{12}$ grain (0.0054 Gm.) induces vomiting and clears the larynx.

A spray of apomorphine in weak solution is sometimes recommended, but the use of the drug in this manner is

hardly safe. It has been found valuable in **whooping-cough** to **relax** spasmodic attacks (Ingram).

Murrell recommends that apomorphine be given in large doses as an expectorant in **bronchitis**. He obtained excellent results from an ointment of: apomorphine, 1 grain (0.065 Gm.); lard or lanolin, 1 ounce (31 Gm.). One-half of this is rubbed into the chest. Murrell also observed the expectorant effect in many by using apomorphine as a spray; it was very marked when the drug was used in large doses. A dose which would act as an emetic, if administered hypodermically, could be used as an inhalation without giving rise to this result. To offset the depressing effects of the drug Bechet recommends strychnine.

Apomorphine hydrochloride has received much praise as a soporific in **insomnia**, $\frac{1}{30}$ grain (0.0022 Gm.) being administered hypodermically on retiring. It has been extensively used for this purpose in **acute alcoholism**. In this condition it should be given in a single dose, likewise of $\frac{1}{30}$ grain (0.0022 Gm.), injected subcutaneously. The object is to give a dose that is large enough, on the one hand, to produce sleep, and, on the other, is sufficiently small so that nausea and vomiting are avoided. Hence, individual susceptibility must be considered. The drug should be given when the patient is in bed, for its effect is very rapid and the patient will usually fall into a restful sleep within five to twenty-five minutes. If no results are observed within one-half hour the dose, according to Douglas, is too small. The effect persists for from one to two hours, but in many cases of insomnia the patient will sleep all night.

Apomorphine is a useful hypnotic when given hypodermically in about $\frac{1}{30}$ -grain dose. Individual susceptibility to the action of apomorphine varies somewhat. To avoid nausea the dose should be as near to the emetic dose as possible without quite reaching it. If it is a little too small it produces no effect whatever, even if repeatedly administered every thirty minutes, as it has no cumulative action. If the dose is a little too large it produces vomiting. Douglas (Alienist and Neurologist, May, 1908).

Warren Coleman and Polk hold, on the other hand, that, while it is best to begin with a small dose— $\frac{1}{30}$ grain (0.0022 Gm.) or less—we can repeat this or give a slightly larger dose within a short time. Further doses should not be given, after vomiting occurs, until several hours have passed. Doses repeated in two or three hours have but little beneficial effect. The drug should not be repeated in patients who are weak. The duration of the hypnotic action is only a few hours, and when the patient awakes his condition is practically unchanged, except in "ordinary drunks." The best results are obtained from apomorphine when it is followed in two or three hours by some recognized hypnotic, as bromide, chloral, paraldehyde, etc. Solutions of apomorphine are unstable, and should be freshly made for use. Old solutions should never be used.

Warren Coleman and Polk also found, after an experience based on 300 alcoholic cases, that the administration of apomorphine to patients in delirium tremens is without beneficial result, and may be attended with danger from its depressing action.

In the treatment of **periodical dipsomaniacs** and in all acute cases of **alcoholism**, the writer advises $\frac{1}{30}$ grain (0.0065 Gm.) of apomorphine hypodermically, to which $\frac{1}{30}$ of a

grain (0.0022 Gm.) of strychnine is added if the heart is acting poorly. The patient should be lying down and basins should be in readiness owing to the rapid action of the drug. Within a few minutes after vomiting has occurred the patient falls asleep and may sleep from two to eight hours. In most instances he awakes refreshed, sober, and rational. The writer has never failed to obtain the hypnotic effect in alcoholics, and but once did the drug fail as an emetic. In many cases $\frac{1}{30}$ grain (0.0022 Gm.) is sufficient, or this small dose may be given in the course of a few hours to prolong the effect of the original dose. Bromides, chloral, or other sedative drugs, if used later, are generally effective in a much smaller dose after apomorphine has been used. The drug should not be given by mouth in these cases, as it is uncertain in its action. Indeed, one of the great advantages claimed for it in alcoholics is that it can be given without objection on the part of the patient when he will obstinately refuse to take medicine by the mouth. Rosenwasser (Med. Record, July 27, 1907).

In laryngeal disorders attended by laborious and suffocative breathing and spasm, known as "**croup**," whether simply catarrhal or membranous (not diphtheritic, since here antitoxin should at once be given), where sedation, expectoration, and relaxation of the vascular tension are helpful, $\frac{1}{100}$ or $\frac{1}{60}$ grain (0.00065 or 0.0011 Gm.) every fifteen minutes produces a happy effect. As relief comes, the interval of administration is lengthened to one or two hours. The same sedative property has enabled apomorphine to allay **spasmodic asthma** and to curtail paroxysms of **pertussis**. When nitrite of amyl or any other nitrite is not available, apomorphine proves of value in **angina pectoris**.

From the fact that this alkaloid pro-

duces emesis by the action through the medullary nerve-centers, and not by irritation of the mucous membrane, it is a good remedy where an emetic is indicated in **catarrhal gastritis, i.e.**, when this disorder is due to the presence of toxic food materials, and washing out of the stomach—a better procedure in general—cannot, for some reason, be practised. It is also useful in very small doses in the **persistent vomiting** of gastrointestinal disorders.

Apomorphine found to relieve **persistent vomiting** due to gastric and duodenal irritation, virtually **gastro-duodenitis**, after everything in the way of oral medicine has been tried ineffectually. In a girl 7 years old in whom retching and straining to vomit had persisted three days, he gave 4 granules of $\frac{1}{67}$ grain (0.001 Gm.) each, dissolved in 20 teaspoonfuls of water, giving a teaspoonful every thirty minutes. Vomiting ceased very soon. When it recurred, apomorphine used in the same manner quelled it at once. Lowery (Amer. Jour. of Clin. Med. Bull., May, 1907).

The value of apomorphine hydrochloride in violent **gastralgia** is attested by Morris, the dose given to produce emesis being used. Balm also found it efficient in a case of persistent **hiccough**. Tull used it with success in **chorea**, a single dose of $\frac{1}{40}$ grain (0.0016 Gm.) causing cessation of the choreic movements; the benefit was kept up by the oral administration of $\frac{1}{30}$ grain (0.0022 Gm.) every three hours, without cessation of the use of Fowler's solution.

In **acute chorea** where the constant violent movements and restlessness of the patient interfere with sleep, a hypodermic injection of apomorphine hydrochloride ($\frac{1}{45}$ grain—0.0014 Gm.) and the "splatch" douche will do more to quiet the patient than all the narcotics, antipyretics, and arsenic. The "splatch" douche consists in the

alternation of jets of cold water (directed in turn over head, neck, chest, trunk, and back), with vigorous massage with hot towels. The success attending this method in very severe cases renders it worthy of more general application. The same treatment is useful in the sleeplessness of delirium tremens. C. A. Wright (Treatment, Jan., 1906).

Apomorphine hydrochloride has been employed for the relief of various **minor hysterical manifestations**. The amounts used varied from $\frac{1}{8}$ to $\frac{1}{20}$ grain (0.008 to 0.0032 Gm.), hypodermically administered, and were never followed by any alarming symptoms (Horsley). Foucher injects $\frac{1}{15}$ to $\frac{1}{10}$ grain (0.004 to 0.0065 Gm.) hypodermically before the onset of and during the paroxysm. It has been found of value as antispasmodic and diaphoretic in **puerperal eclampsia** by Kitchens, a result readily accounted for by the muscular relaxation, including that of the vascular muscles, to which the drug gives rise.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

APPENDICITIS.—DEFINITION.—An inflammation of the vermiform appendix, frequently complicated with ulceration and perforation of its coats, caused by microbic infection, but which may also originate from irritation produced by hardened fecal masses, foreign bodies, or traumatism.

Two forms of appendicitis, the *acute* and *chronic (relapsing or recurrent)*, are now generally recognized.

The writer calls attention to a group of cases in which, though the appendix is a factor, the chief irritative lesions are fibroid degeneration and syncongestive appendicitis. A second, larger group, with symptoms

in the appendix region, but not including the appendix, appears to depend upon a variety of spinal irritative lesions, with efferent impulses sent out both to the cerebrospinal nerves and sympathetic nervous system, and possibly to the automatic centers. Pressure about $1\frac{1}{2}$ inches to the right of the navel and a trifle below, deeply enough to bring out the response from the right group of lumbar sympathetic ganglia, affords definite evidence that one is to look to the appendix for the source of irritation, provided the left group of sympathetic lumbar ganglia is not hyperesthetic. This point of tenderness situated several inches away from McBurney's point relates to a chronic irritative lesion of the appendix. Surgical judgment in addition requires one to determine if the patient is one with neurasthenic habit and relaxation of peritoneal supports with chronic enteric toxemia. R. T. Morris (N. Y. Med. Jour., May 20, 1916).

ACUTE APPENDICITIS.

SYMPTOMS.—Whether catarrhal or ulcerative, the attack presents itself usually in a previously healthy person and begins with sudden intense pain in the abdomen, often beginning in the region of the umbilicus, and later localized in the right iliac fossa at a spot $1\frac{1}{2}$ to 2 inches from the anterior superior spine of the ilium toward the umbilicus (McBurney's point), and increased by pressure. At first paroxysmal, it finally becomes constant. This is the most important diagnostic sign when associated with the other symptoms.

The writer was able to palpate the appendix in 250 of 510 men who had never had any appendiceal symptoms. He was surprised to find that the appendix was tender in 58.4 per cent. of the 250 instances. Orłowski (Archiv f. Verdauungskrankheiten, April, 1911).

The pain may radiate from this point toward the umbilicus, the epigastrium, the groin, and the testicles. It may be felt in other parts, elsewhere on the right side of the abdomen, the pelvis, loin, or on the left side, and may even be located in the left iliac fossa. It is important to bear in mind, moreover, that, as stated by Sturmdorff: while it is true today, as it was twenty years ago, that a typical McBurney point may be present in a typical appendicitis, it is equally true that appendicitis may exist in the absence of a McBurney point, and, most important: a typical McBurney point may be present in the absence of appendiceal involvement.

Pressure on the corresponding point on the opposite or left side will elicit, according to Rovsing the typical pain at McBurney's point in case of appendicitis, but not in other abdominal affections. It was never found unless there was some affection of the cecum or appendix.

Case of appendicitis in a girl of 8, with pain at a point on the left side, symmetrical with McBurney's point appearing on the second day. There was no pain on the right side. Laparotomy revealed a ruptured abscess on the left side. Pain in this location may also be due to an appendix on the left side. Proust and Paris (*Rev. de gynéc. et de chir. abd.*, xxiii, 187, 1914).

The writer found that traction on the right spermatic cord produced pain in 12 out of 15 cases of appendicitis. The pain is probably due to irritation of the peritoneum about the internal ring. Ten Horn (*Zentralbl. f. Chir.*, Oct. 3, 1914).

The writer observed several cases of acute appendicitis in which the pains and contracture were more pronounced in the inferior lumbar region than in front. The appendicitis was retrocecal in these cases. This form is more common in children than in

adults. The painful point in the lumbar region should be sought with care in conditions suggesting appendicitis, especially when there is not much to be noted in front. He has found this painful point in 30 per cent. of his cases. Brun (*Presse méd.*, Jan. 16, 1919).

Illoway has noted that invariably (often verified by a subsequent operation) only when appendicitis was present, whether as the primary malady or as a secondary involvement, did the flexion of the thigh on the trunk give rise to a feeling of pain or a sensation of soreness deep down (according to the patient), and even when this was not so marked the rapid extension would cause an accentuation of it.

This pain, which is augmented by pressure, deep abdominal respiration, and movements of the right thigh, may be absent or have entirely disappeared after suppuration or gangrene of the appendix has occurred.

Tenderness over the right sympathetic lumbar ganglion ($1\frac{1}{2}$ inches from the navel on a line with McBurney's point) is a diagnostic sign in appendicitis in addition to the well-known McBurney's point, according to our associate editor, R. T. Morris. In the early stages of an acute infective process of the appendix the right lumbar ganglia are tender and the left lumbar ganglia are not tender. (The left lumbar ganglia may be described for diagnostic purposes as lying an inch and a half to the left of the navel.) Under these circumstances, the point here described is of secondary importance, while McBurney's point is of prime consequence: (a) When an acute inflammatory process of the appendix has subsided, leaving a mucous inclusion or scar-tissue, there may be no tenderness on pressure at McBurney's point, but there is tenderness at the point here described, and no tenderness at the point of the left lumbar ganglia. (b) When the appendix is undergoing a normal involution process, with replacement of its lymphoid coats by connective tissue,

digestive disturbances and various local neuralgias may be due to nerve filaments entrapped to the new connective tissue. There may be no tenderness at McBurney's point, but there is persistent tenderness at the point here described. There is no tenderness at the point of the left lumbar ganglion. When the appendix is congested without the presence of infection, as in many cases of loose kidney, there may be little or no tenderness at McBurney's point, but there is persistent tenderness at the point here described. There is no tenderness at the point of the left lumbar ganglia. Under these conditions, the point here described is of primary importance, while McBurney's point is of secondary or no significance. It will be found useful in differentiating between appendiceal and pelvic irritations. If it is alone tender, it means appendix trouble. If both right and left lumbar ganglia points are tender, it signifies pelvic disorder. If neither of these points are tender, the abdominal irritation must be looked for somewhere higher up than the pelvis or the appendix. EDITORS.

In appendicitis fever is always present. If the appendix is in the pelvis the pain is likely to be left-sided. Suddenly subsiding pain followed by a chill points to gangrene, while exquisite tenderness denotes the presence of pus. Deaver (N. Y. Med. Jour., Feb. 5, 1916).

The writer found that in 90 per cent. of all appendicular troubles, or those involving an inflammatory condition of the appendix, the pain is increased when the patient is turned to the left and diminished when he is turned back on his right side. The pain is not so intense when the patient is on his back as on the left side. Blaisdell (Arch. of Diag., July, 1917).

Oversensitiveness of the skin over the diseased area may also be present and persist until convalescence begins. It depends upon tension with the appendix. It may be absent in attacks after the first, if the first attack was of sufficient severity to destroy nerve-tissue in the wall of the appendix.

Hyperesthesia in the right lower quadrant is usually present in the early stages, although it may disappear once the appendix has perforated. Rigidity of the lower half of the right rectus muscle is almost always present, as is tenderness on pressure in this region. Most difficulty is encountered where the obstructed appendix is lying high up in the retrocecal region, but even here some hyperesthesia of the skin above McBurney's point, together with tenderness in the lumbar region posteriorly, and a normal urine, incriminate the appendix. The importance of making a diagnosis on the local signs cannot be overemphasized, because in these cases to wait for changes in the temperature or the pulse-rate so often means delaying until gross pathological changes have supervened and the danger zone been entered. Wilkie (Edinb. Med. Jour., Nov., 1920).

Epigastric pain, of a reflex character, has also been observed. If adhesion to the bladder has occurred, pain in the vulva may be caused.

Pain in the cecum is a very common condition in patients with affections of the alimentary tract and is often mistaken for appendicitis. To palpate the cecum, the radial border of the right hand in forced pronation, with the fingers directed toward the pubes, is used to exert deep pressure in the right iliac fossa. In doing so, to and fro movements from the inner margin of the cecum outward are executed, the thumb resting for support against the outer portion of the iliac crest. Repetition of the procedure at different levels permits of ascertaining the situation, margins, shape, and consistency of the cecum. Among 123 patients the cecum was palpable in 54 and tender in 40. Among the remaining 69, 22 complained of marked pain, radiating toward the sigmoid or epigastrium, upon pressure over the cecum. The cecum was thus abnormal in 66 cases, or 63 per cent.; according to Glénard the normal cecum is neither tender nor defi-

nately palpable. A relationship seems to exist between cecal tenderness and such liver affections as hepatoptosis, hepatic enlargement, gall-bladder pain in the absence of actual attacks of colic, cirrhosis, etc. Of 50 patients with definite hepatic disease, 32 had a palpable or tender cecum. Of 108 patients with gastric disorders causing objective signs, 72 had an abnormal cecum. L. Pron (Bull. de l'Acad. de Méd., Feb. 5, 1918).

Constipation is present in the majority of cases. Nausea and vomiting are also present in most instances, but they do not always furnish information as to the seriousness of the case. They may occur coincidentally with the attack or shortly after. Nausea and vomiting are purely reflex, but are very constant symptoms, being due to irritation having its origin in the appendix. They may cease when the stomach is emptied of its contents, but may return when other causes are brought into play, as, for instance, peritonitis due to perforation.

There are gastric crises which simulate appendicitis. These crises are connected with lengthening and dilatation of the stomach when not due to pyloric spasm. Differential diagnosis may be speedily made by means of the pain signal of the author. To elicit this, the patient is placed erect before the physician, who delimits first, on the line between the umbilicus and the xiphoid cartilage, the region where pain is most acute on deep palpation. When this zone is found, an assistant places his forefingers on the sensitive point and presses down so as to elicit pain. Then from below upward, beginning above the pubis, the physician raises the abdominal contents by profound pressure with his thumbs placed end to end on the median line till he reaches the umbilicus. The patient states when he ceases to feel pain from the deep pressure; that moment signalizes the lifting of the lower border of the stomach and demonstrates that the pain does not

come from an inflamed appendix. Leven (Presse méd., June 21, 1911).

The tongue is usually coated. The respiration is not materially influenced unless peritonitis develops, when it becomes costal.

The pulse and temperature are apt to vary considerably in different cases and do not bear a definite or constant relation to the severity of the disease, though a sudden rise of temperature, or of the pulse rate, or both generally indicate extension of the morbid process to the peritoneum. A slow pulse is thought by Kahn to indicate that gangrene of the appendix is present.

A difference between the axillary and rectal temperatures is noteworthy in appendicitis. Normally, the rectal is 0.6° C. higher than the axillary temperature, but in appendicitis this difference is greatly increased, even to 1.4° C., due to the hyperemia of the pelvic viscera.

Slow pulse as a symptom of latent or incipient gangrene in appendicitis has been so frequently met in the writer's series of cases that in the last 6 he made the diagnosis before operation on this symptom alone. It is true that cases are sometimes seen with tachycardia, but the writer does not recall encountering bradycardia in a case of appendicitis that did not present gangrene. Of course, the normal pulse of the individual must be known to avoid mistakes. M. Kahn (Jour. Amer. Med. Assoc., Dec. 15, 1906).

The temperature in the axillæ in acute appendicitis is markedly different from that of other regions. This is probably due to the fact that the right sympathetic is irritated in the beginning of acute appendicitis, and that the irritation involves the left sympathetic. Hönck (Deut. med. Woch., Aug. 27, 1908).

Anorexia and digestive disorders are rarely absent. Diarrhea and constipation may alternate, but the latter is more

frequently observed, especially at the onset of the attack. Jaundice is occasionally noted, especially in severe cases. Reichel, among 165 of his cases of appendicitis, noted jaundice in 18; of these, 10 resulted fatally.

Series of typical cases illustrating the frequent coexistence and interrelation of colitis and appendicitis. This emphasizes the need of more thorough attention to the colon before rushing chronic cases to operation. It also emphasizes the great necessity of after-treatment of the colon in cases of chronic appendicitis associated with colitis (and a large proportion are so associated). It also points to the inadvisability of removing the appendix through the smallest possible opening, and of not exploring the whole abdominal cavity when there have been chronic symptoms. M. V. Tyrode (Boston Med. and Surg. Jour., Jan. 4, 1912).

There can be a cecal stasis quite independent from appendicitis, ileostasis or constipation of cecal origin. This is proved by radiographic plates which show a permanent shadow over the cecal area which may be present for weeks, although the progression of the fecal mass onwards remains perfectly normal. This stasis is never due to a functional cause, but is generally attributable to peritoneal adhesions. Laxatives have little, if any, effect on it. E. Schlesinger (Deut. med. Woch., May 9, 1918).

Rigidity of the right abdominal wall is generally present, but circumscribed rigidity over the region of the appendix occurs in about one-half of the cases. The degree of rigidity usually corresponds with the intensity of the local inflammation. Tympanites is often present if there be peritoneal inflammation of the adjacent intestinal coils.

While ordinarily rigidity of the right rectus is a reliable guide to appendicitis, in some cases rigidity of the right external oblique is present instead. These cases are mild, many

patients being up and about at the time, but a high polynuclear count exists. In over 20 cases with rigidity only of the right external oblique, the appendix was retrocecal or retrocolic. Randall (Jour. Amer. Med. Assoc., June 5, 1915).

If the case be one of simple catarrhal appendicitis, the above symptoms continue two or three days, and the patient gradually recovers.

The differential blood-count and its relation to the total leucocytosis are today the most valuable diagnostic and prognostic aids in acute surgical diseases that are furnished by any of the methods of blood examination. They are of value chiefly in indicating fairly consistently the existence of supuration or gangrene, as evidenced by an increase of the polynuclear cells disproportionately high as compared to the total leucocytosis. The greater the disproportion, the surer are the findings, and in extreme disproportions the method has proved itself practically infallible. If the leucocytes number more than 14,000, and especially if the polynuclears are more than 70 per cent., an early operation is indicated unless there be strong reasons for not doing so.

In general, the blood picture is an expression of the virulence of the infection, while the leucocytosis corresponds to the degree of peritoneal irritation and the capacity of the individual for reaction. Increased leucocytosis with a normal or nearly normal blood picture gives a good prognosis. The higher the blood picture mounts, the more severe the infection and the more serious the prognosis. If the leucocytosis is increased it is a favorable sign (good resistance), while a low leucocytosis with a high blood picture is always a serious sign. A simultaneous, moderate increase of the curves is a favorable sign, as is an increase of one or the other curves or an intersection of the curves. The most unfavorable cases are those

of peritonitis with a very high blood-picture curve and a normal or subnormal leucocytosis. If after operation the blood-picture curve is low and the leucocytosis high, the tendency is to improvement, the organism gaining the upper hand in the fight against the infection. Kohl (Mitt. a. d. Grenzgeb. d. Med. u. Chir., Bd. xxii, S. 542, 1911).

Variations from the above course are met with. The disease may come on insidiously, and fever or pain be totally absent.

The appendix may be the seat of gross lesions, although the patient has never had a recognizable attack of appendicitis. In acute appendicitis the physical signs may be very slight, in rare cases absent, so that there may be little indication of the serious condition of the patient. Chronic appendicitis may simulate gastric disease with remarkable fidelity. H. J. Paterson (Med. Record, Aug. 19, 1911).

Although such an insidious onset is occasionally met with in adults, it is most likely to occur in children. Occasional colicky pains are sometimes the only early signs furnished, these being followed by the typical symptoms described above.

Localization of the appendix tenderness in a distressed baby may be quite difficult. The acute attack is attended by distress, restlessness, vomiting, crying, and abdominal soreness. So do acute digestive disturbances; but in the sleeping or restful moments, slight, and then greater, pressure over the abdominal surface forms the crucial test. Rectal examination aids. Violent acute attacks often follow a chronic insidious preparation. Marvel (Arch. of Pediat., May, 1912).

Out of 200 cases in children under 13 years, 74 were chronic and recurrent, and 126 acute. Among the acute were 86 gangrenous cases, of which 45 had some peritonitis. The acute cases gave a mortality of 15

per cent. The classical symptoms were present in practically all cases, but frequently one of them predominated over the others. Diarrhea was prominent in 6 cases, 4 of which were fatal; in all 6 there was diffuse peritonitis. This type of case is likely to be mistaken for simple enteritis. Pain and frequent micturition characterized 4 cases. The percentage of cases with diffuse peritonitis is much greater in children than in adults, with gangrene and perforation in a large proportion. The omentum is likely to be very small and does not tend to limit the inflammation. Every case operated in the first 2 days of illness recovered. Gray and Mitchell (Brit. Med. Jour., Feb. 21, 1914).

In children clean cases of appendicitis (those in which it is not necessary to insert a drain) are unusual. In reviewing the case records at the Samaritan Hospital two years ago, the writer found that at least 90 per cent. of patients under 15 had peritonitis, either local or general, and that the mortality was four times greater than in a corresponding number of adult cases. In Deaver's series 85 per cent. had abscess formation and the mortality was 4.6 per cent. These facts demonstrate the importance of early diagnosis of the condition in children. J. O. Bower (N. Y. Med. Jour., Sept. 21, 1918).

Slight appendicular lesions may be accompanied by alarming symptoms in hysterical patients, or in those mentally and physically below par. Renal and cystic phenomena, including renal colic, painful micturition with tenesmus, may also occur.

The writer describes 6 cases in Italian literature and 2 from his own experience in which reflex nervous phenomena, kidney colic, pain during micturition, bladder tenesmus, cystalgia, smarting in the urethra, or priapism were the first signs of trouble which later proved to be appendicitis. The inflammation in the appendix evidently acted on the vesical, renal, hypogastric,

or pubic plexus, inducing functional disturbance. F. de Meo (*Annales des mal. des org. genito-urin.*, Dec. 1, 1910).

Chills sometimes occur, but they usually coincide with gangrene of the appendix or with the formation of a local or metastatic abscess. When an abscess or a fibrinous exudate forms about the appendix, it may usually be detected by palpation, being fixed and smooth, surrounded by an area of tympanites. Rarely it may fluctuate, especially when large. Any considerable pressure should be avoided, since it might cause rupture of the abscess. Rigidity usually disappears when such an abscess or the infected focus becomes encapsulated.

Progress toward perforation either into the general peritoneal cavity or into a cavity formed by adhesions is probable when, on the third day, or even earlier, after the onset of the symptoms, there is a localized superficial edema, indicating deep suppuration, and when a doughy mass is felt at the seat of pain, which mass gradually assumes shape to the touch, unless distended intestinal coils, shown by local tympanites, or the tension of the abdominal walls make its detection impossible. Perforation is also often indicated by a cessation of pain and an increase in the tension and frequency of the pulse rate.

The writer has found constantly in all his cases that after the first onset of symptoms the pain subsides under repose and ice, but that suddenly a paroxysm of pain returns. Although this soon subsides again, this abrupt return of pain, though not due to imprudence, is a sign of perforation sufficiently certain to indicate immediate operation. Delbet (*Presse médicale*, June 3, 1908).

If suppuration is present and perforation occurs on the fourth or fifth day,

i.e., after the adhesions have formed, the symptoms do not, as a rule, vary from those enumerated. When, however, they do not assume a graver form during the first four days, the presence of protective adhesions is likely. The presence of general rigidity over the whole lower abdomen, even with little rise of temperature and slight increase in the pulse rate, indicates perforation with secondary abscess in the pelvis.

When the symptoms are marked and a tumor cannot be felt, perforation has probably occurred before the adhesions were sufficiently perfect to protect the peritoneal cavity.

If perforation has occurred early, *i.e.*, while the adhesions were still imperfect, there is usually a chill and vomiting; shock, more or less profound; diffuse, marked pain, instead of the localized pain; acceleration of the pulse; an increase of temperature of 2° or 3° F.; scanty and dark urine, showing high specific gravity.

Perforation is also accompanied by distention of the abdomen, and symptoms of grave diffuse peritonitis appear, followed by collapse. Dullness, especially in the right iliac fossa, affords an early clue to the presence of pus.

In *fulminating appendicitis*, termed such owing to the rapidity with which the disease progresses, the peritoneum may be involved within a few hours. Again, in the midst of what apparently is a mild case, abscess, gangrene, and perforation may suddenly appear with all their disastrous sequelæ. This indicates the necessity of giving the greatest attention even to apparently benign cases.

When appendicitis occurs during pregnancy the attack is usually sudden and begins with abdominal pain, which gradually becomes localized; this is fol-

lowed by the typical symptoms. This condition must be carefully differentiated from tubal pregnancy. The prognosis is grave. The chances of abortion following operation are not great, provided a speedy operation is done. In the last half of the pregnancy the condition is much worse and operation is more difficult.

During the first three months the treatment should be the same as in the non-pregnant state, but if immediate operation is not performed and the patient is carried through the attack without removal of the appendix this should be done soon afterward, since the risk of recurrence later in pregnancy at a more dangerous period is great. After the third month the treatment should be immediate removal of the appendix as soon as the diagnosis is made, since the high mortality of this complication is due to delay. This applies especially to the later months when, owing to the greater congestion and increased intra-abdominal pressure, the inflammatory changes are apt to be very marked, with early perforation. A. H. Bill (*Cleveland Med. Jour.*, Aug., 1911).

Review of the literature of 480 cases coming under the writer's observation. Appendicitis is a comparatively frequent condition in pregnancy (1 to 1000), about 2½ per cent. of all women suffering from the disease being pregnant. It would appear, however, that pregnancy does not predispose to appendicitis, although it may favor recurrences and exert an unfavorable influence on its course. In view of the high mortality of severe cases and the excellent statistics of early operation, conservative treatment should be resorted to only for the milder forms, where the patient can be kept under supervision. H. H. Schmid (*Deut. med. Woch.*, Nu. 29, 1911).

Out of 10 women who had had, prior to conception, repeated attacks of appendicitis, 6 had recurrences in

their first pregnancies. Four were operated early in the attacks, without any post-operative disturbances. In the others drainage was required. Perforation of the appendix and peritonitis during pregnancy are severe because protective adhesions are less likely to form; inflammation is more intense owing to the greater vascularity; the peritoneum of the upper abdomen is more often involved; the infection spreads under and around the uterus, and drainage is interfered with, muscular rigidity and tympany predispose to pneumonia and pleurisy; obstruction of the bowel is more apt to occur, especially in the later months. If an abscess becomes walled off, it is apt to rupture in labor. In operating between the first and fifth month a right rectus incision is suggested, to inspect the tubes. After the fifth month a higher incision and liberal drainage are advised. If abortion is inevitable the uterus should be emptied. W. L. Crosthwait (*Texas Med. News*, xxv, 337, 1916).

During examination gentle manipulation is necessary, lest an abscess be present and the adhesions be delicate and unable to stand the traction or pressure (McBurney).

The location, direction, and extent of the appendix have an important bearing on the clinical history of appendicitis, considering the variations of the appendix in length, direction, and location and the varying site of the cecum.

Auscultation of the lungs and heart sometimes affords information.

Examination through the rectum is of value in determining the presence of pus in advanced cases, especially in children. In the earlier stages this procedure is not very helpful.

High palpation of the right iliac fossa by rectum elicits tenderness and pain in the McBurney region in children. The examining finger must be introduced quite painlessly. This can

always be done if patience is exercised. The valuable diagnostic point is that the patient complains of no discomfort until the finger reaches the right iliac fossa, when a sharp pain in the vicinity of McBurney's point is elicited. F. L. Wachenheim (*Arch. Pediat.*, xxxiii, 197, 1916).

Examination of the urine may assist in the location of the inflammatory process and in determining the activity of metabolic processes. Glycosuria has also been observed.

Severe appendicitis cases show a marked decrease in urea excretion, replaced in convalescence or soon after successful operation by a marked rise. Low urea excretion, with alimentary glycosuria and urobilinuria, imply a grave prognosis. Study of urea curves facilitates diagnosis between lesions of the appendix and the uterine annexa. J. Duvergey (*Paris méd.*, May 10, 1913).

Children often suffer from appendicitis, the frequent gastrointestinal disorders to which they are subject being not infrequently related with a diseased appendix. The symptoms do not differ from those of appendicitis in adults, but their development is apt to be more rapid.

To facilitate diagnosis in doubtful cases in infants and young children that cry on examination, Crile gives the child "twilight" ether anesthesia. Under deep pressure there is a distinct muscle reflex on the right side when appendicitis is present, but none on the left. Moreover if pressure is made when the anesthesia has faded to the subconscious state, there is a significant pain response. EDITORS.

A practically pathognomonic sign in children is that almost invariably the little patients place their hands in the region of the appendix to ward off manipulation in this region. Pain present in the lower quadrant with evident tenderness, pain, and resistance in the right quadrant, appendicitis, in other words, and without any marked evidence of

abdominal distention, signifies an excess of free fluid in the pelvic cavity, varying in character from a serous to a sero-purulent or purulent nature, although the appendix and abscess, if present, are thoroughly walled off. J. F. Erdmann (*Archives of Diagnosis*, July, 1908).

In an analysis of 500 cases the writer insists on the importance and frequency of appendicitis in childhood. The number of cases increases in frequency with age, from birth to puberty, and it is more common in males. The course is more often severe than in adults. There is less tendency to formation of strictures, but fecal concretions are more frequent. H. C. Deaver (*Jour. Amer. Med. Assoc.*, Dec. 24, 1910).

Appendicitis is the commonest and most important surgical disease of the abdomen in childhood. Most of the cases occur between the ages of 5 and 15 years. In children the appendix is comparatively larger, lymphoid tissue is more abundant, and there is a shortness and lack of development of the omentum. The causes of appendicitis are similar to those of adults, careless feeding and catarrhal diseases probably taking the lead. The difficulties in making a diagnosis in infant children are great. Pain, a constant symptom, is often ascribed to an ordinary gastrointestinal attack. Nausea and vomiting may be absent even in peritonitis. A rise of temperature is so common in children that this sign is not absolutely reliable. Fever in appendicitis usually begins some time after the initial pain. A sudden drop is a danger signal, and may mean gangrene or perforation. In gastroenteritis vomiting is earlier and precedes the pain. Abdominal pain is less severe, and true abdominal rigidity is absent. It is a grave mistake to treat appendicitis with a purgative. Harold Collinson (*Practitioner*, July, 1911).

The large mortality from appendicitis in children is not due to any special anatomical condition or peculiarities, nor to greater difficulties of diagnosis. It is chiefly due to the fact that patients are subjected too late to the proper treatment, *i.e.*, operation. The delay is ascribed to

the public's lack of knowledge of early symptoms and the necessity for operation in children and to our inability to interpret symptoms of chronic appendicitis in the true sense. We are too much accustomed to regard gastrointestinal affections as peculiar to childhood, and not as a frequent sign of serious disease. Salzer (*Wiener klin. Woch.*, Nu. xx, 1911).

Frequent and painful urination in children may be an early sign of appendicitis. Also, if a finger is introduced in the right inguinal canal the muscles contract about it if the appendix is inflamed and the cord is found tender. There is relaxation of the sphincter ani muscle when the pouch of Douglas is being invaded. Lanz (*Zentralbl. f. Chir.*, Nov. 28, 1914).

Closer co-operation between parents and surgeons would give the child with a "belly ache" a better chance to live. Of 404 cases, 37 were in children with an operative mortality of 5.4 per cent. Of the 367 adult cases of appendicitis, there was also an operative mortality of two, or 0.54 per cent. The most constant symptom of acute appendicitis in children is leucocytosis, which ranges between 9000 to 34,000, with the polymorphonuclears between 72 and 92 per cent. The high mortality among children seems to be due to the fact that the early symptoms are not clear-cut and defined as in adults. Purgation in cases of appendicitis in children is one of the chief causes of the frequency of perforative appendicitis. J. C. Motley (*Jour. Amer. Med. Assoc.*, Nov. 4, 1916).

In 80 cases of appendicitis in infants under 2 years of age collected from literature, 20 cases under 3 months of age, among which were 2 possible instances of prenatal appendicitis. In children from 3 to 6 months of age there were 6 recorded cases; 11 cases in children from 6 to 12 months; 40 cases in children from 1 to 2 years. Of this number 25 were males, 8 females and 7 were without

record of sex. The blood examination in almost every case shows a polymorphonuclear leucocytosis. Tenderness at McBurney's point, if it can be elicited, is of diagnostic importance. When there is palpable resistance on the right side, in the presence of other symptoms, the diagnosis of appendicitis should be suspected. I. A. Abt (*Arch. Pediat.*, xxxiv, 641, 1917).

Rapid progress to gangrene and perforation is much more common before the fifth year than later in life as evidenced by the fact that 73 per cent. of the writer's patients of 5 years or under perforated in contrast to 28 per cent. in children between 10 and 15. The gravest danger to these little patients lies in the fact that parents are allowed to think stomach-ache a normal event in children's lives and to believe that purgation is a panacea. Porter (*Calif. State Jour. of Med.*, Jan., 1918).

Ptomaine poisoning or acute gastrointestinal colic is the usual diagnosis in a large percentage of cases that come to operation; in such cases, the presence of diarrhea, absence of leucocytosis, cessation of vomiting following stomach lavage, and history of some indiscretion in diet, make the diagnosis of toxemia evident. Acute pyelitis is often associated with abdominal pain; the dominant symptom is usually fever and correct diagnosis may be reached by the microscopic examination of a centrifugal specimen of urine. A possible vaginitis should be excluded. Intussusception in children may be ushered in by a sudden cry. A sausage shaped mass that varies in position, the presence of characteristic vomiting of overflow intestinal obstruction, with blood-stained mucous stool, absence of rigidity, leucocytosis and temperature are diagnostic features in this condition. In pneumonia, points to be remembered are the respiration, pulse ratio, and intermittent spasticity of the recti, herpes and high leucocyte count. In acute perforation of the stomach, the pain is most

severe; there is marked abdominal rigidity and patients vomit immediately the drug or laxative given by mouth; in early cases temperature is usually subnormal and pulse comparatively slow. In acute pancreatitis, a history of preceding attacks of colic points to a diagnosis of pancreatic inflammation. Abdominal tuberculosis of one type or another is found in 90 per cent. of cases of appendicitis in children preceded by attacks of similar nature. J. O. Bower (N. Y. Med. Jour., Sept. 21, 1918).

Bastedo sign has been found useful by some observers and valueless by others. It consists, after carefully cleansing the bowel, in distending it with air through a rectal tube. If the appendix is diseased pain is complained of at McBurney's point.

Bastedo's inflation of the colon should be regarded merely as an aid in the diagnosis of appendicitis, history and physical examination being far more valuable. The writers have seen no positive reactions in normal individuals. The method is unsafe and rarely useful in acute appendicitis, and it is in no sense pathognomonic of chronic appendicitis. Goodman and Lüders (Amer. Jour. Med. Sci., Sept., 1914).

DIAGNOSIS AND COMPLICATIONS.—Although the three cardinal symptoms: pain, tenderness, and rigidity, render the diagnosis of acute appendicitis comparatively easy, the fact remains that many conditions simulate it and may, therefore, lead to a mistake. Yet, it should be remembered that several of these disorders may actually be present as complications, as several examples submitted below will show.

Quite prominent in this connection, of course, are disorders of the gastrointestinal canal: intestinal obstruction, volvulus, perforation or foreign body, inflammation of Meckel's diverticulum, and acute infections of the gall-

bladder. The fact that some of the symptoms of the latter and of hepatic disorders, especially jaundice, as we have seen, may occur as complications of appendicitis serves further to complicate the situation. Several observers have come to the conclusion that cirrhosis of the liver may be one of the complications of appendicitis.

Occasionally a diarrhea or dysentery may usher in the scene, and this fact should never be forgotten. Usually the bowel movements are torpid. Conditions simulating appendicitis are severe colic from acute indigestion, pneumonia, typhoid fever, renal colic, inflammation of the gall-bladder, gastric ulcer, and epididymitis. M. H. Fussell (N. Y. Med. Jour., Jan. 22, 1910).

In 7 personal cases the appendix was attached by adhesions to the right ovary, hanging between the cecum and the ovary like an ordinary hammock. While in these cases the appendiceal symptoms predominated, some of them were manifestly referable to the ovaries. McKinley (Med. Record, Dec. 2, 1911).

Case of persistent patent Meckel's diverticulum simulating appendicitis. Operation showed the presence of an abscess. The localized tumidity and tenderness were located rather higher and nearer the middle line than usual. Glover (Lancet, Mar. 3, 1917).

Gastric disorders may, in fact, be traced directly to a chronically inflamed appendix, and as such to acute exacerbations of appendicitis. Gastric ulcer—with marked gastric pain after taking food; eructations, hyperchlorhydria, etc.; nausea, vomiting and even hematemesis, and blood in the stools; melena—has also been diagnosticated where the causative lesion, as demonstrated by the normal condition of the stomach and the result of removal of diseased appendix, lay clearly in the latter.

The writers observed hematemesis in a case of true appendicitis. Chains of small glands in the omentum and mesentery pointed to a stream of infection carried up the omentum and deposited at the pylorus. Outland and Clendenning (*Amer. Jour. Med. Sci.*, Feb., 1917).

After studying 1400 cases, including 300 designated as pseudoappendicitis, the writer contends that faulty differential diagnosis very often is due to perimetritis, also pyclitis or pyelonephritis, renal colic, enterocolitis, and acute inflammation of the cecum. He urges that it is not sufficient to determine pain at McBurney's point, spastic contractions of isolated portions of the intestine, etc. In many cases, spastic contractions will disappear during narcosis and before the beginning of the operation. Intestinal spasms are frequent and often mistaken for chronic appendicitis. Such neuroses require no operation, while **atropin**, given 3 weeks, is efficient: 0.001 to 0.0015 Gm. ($\frac{1}{44}$ to $\frac{1}{45}$ grain) of atropin sulphate in pills each day. In severe cases, a 1:1000 solution of atropin sulphate (for 5 days, 3 times 4 drops; next 5 days, 3 times 8 drops; then 12 drops 3 times daily, and back to 4 drops). E. Liek (*Mittheil. a. d. Grenzgeb. d. Med. u. Chir.*, xxxii, No. 2, 1920).

Floating kidney with torsion of the ureters, nephritis with hematuria, renal or hepatic colic, ovaritis, extra-uterine pregnancy, ovarian cyst with twisted pedicle, pelvic cellulitis, dysmenorrhea, inflamed undescended testicle, epididymitis and hernia, incipient or strangulated, have all caused confusion.

It is difficult to distinguish correctly between appendicular inflammation and stones in the kidney or ureter. The urinary system is often affected in appendicitis, and in such cases hematuria will appear.

The intestinal stasis in the flexura coli forms a hard mass of the feces, which through pressure upon the left kidney or its vessels produces hema-

turia. Von Frisch (*Wiener klin. Woch.*, Jan. 4, 1912).

The writer operated for combined chronic appendicitis and hernia in 53 children. When a child has pains from an inguinal hernia, or undescended testicle, appendicitis should always be suspected. One may preferably operate separately on the hernia and the appendix, except in small children not in an acute stage. Veau (*Bull. de la Soc. de Pédiat.*, May 5, 1914).

The possibility of hematuria during acute or chronic appendicitis, independently of any genitourinary lesion, is pointed out by the writers. In chronic cases hematuria may be the first and only symptom, occurring suddenly after a strain, sudden exposure to cold, etc. Pain simulating renal colic may or may not coexist. Carlier and Leroy (*Prov. Méd.*, xxvii, 102, 1914).

A psoas abscess, fecal impaction in the right iliac region, tumors, lymphadenitis, aneurism in this area, tabetic crises in the abdomen, lead colic, pneumonia, pulmonary abscess, and pleurisy have all proven misleading. The two latter disorders may, in fact, be associated with appendicitis, *i.e.*, appear as one of its complications. According to Sonnenberg, the greater number of cases in which there are lung complications originate from emboli; Gussenbauer has had a similar experience. In the hospital at Moabit, out of 740 cases 28 had some lung complications, and, of these, 14 were cases of thrombosis, and in the private clinic out of 260 cases 19 had some lung complication.

In pleurisy complicating appendicitis the germs from the appendiceal cavity pass to the peritoneum, thence are carried to the pleura. The appendicitis may spread upward behind the colon, the liver, to the diaphragm and the pleura. The signs of pleurisy usually come on when the appendicitis begins to subside. The prognosis is grave, and the treat-

ment consists in an operation for empyema, which should be promptly performed. Barba (*Riforma medica*, Nov. 24, 1906).

The writer observed several cases in which râles, congestion in the apices, and other symptoms of pulmonary tuberculosis fluctuated with exacerbations of chronic appendicitis, and disappeared completely after appendicectomy. The pathologic condition of the appendix was discovered accidentally at an ovarian operation in one case. In three of the cases, consultants did not accept his diagnosis until two of the apparently doomed patients regained their health after the appendicectomy. Schoull (*Paris méd.*, Oct. 12, 1918).

Thrombosis in the veins of the jejunum or other neighboring structures may not only give rise to acute symptoms recalling those of appendicitis, but it may also occur as a complication of the latter. Phlebitis, edema, obstruction of the portal system and of the mesenteric, omental, gastric, iliac, and other veins have also been traced to this cause.

Case in which appendicular abscess followed phlebitis of the external jugular vein. No untoward symptoms developed until the eighth day, when the temperature rose to 105° and the pulse to 140. There was also a chill. The drainage, the appendix not having been removed, was free, and there were no signs of extending peritonitis. The drainage had a fecal odor, but not more so than at the time of the operation, and there was no fecal matter in the drainage. The patient complained of a stiff neck, with soreness in the left side of the neck. On the following day the pain in the neck was much more severe. The writer found the external jugular hard like a cord, and very painful to the touch. Just above the clavicle there was some perivascular inflammation. The head being immobilized, the inflammation receded and disap-

peared. Richards (*Med. Record*, Dec. 23, 1911).

From the standpoint of differential diagnosis the *main* disorders which tend to cause confusion and the symptoms which help to identify them are the following:—

Intestinal Obstruction.—In this disorder the rise of temperature occurs late. Stercoraceous vomiting is observed in serious cases. Volvulus generally presents itself in children. There is more distention and no abdominal rigidity. The pulse and temperature are normal in the early stages. Intestinal obstruction may, however, attend or follow appendicitis.

The writer studied 44 cases of obstruction of the intestine during or after appendicitis, including 14 in which the ileus was due to atony of the bowel, 10 with broad adhesions and 18 with narrow, 1 with an inflammatory tumor, and 1 with stenosis from ulceration in the cecum. These appendicitic cases formed 17.9 per cent. of the cases of ileus in his experience in the last twenty years, but only 1.8 per cent. of the total cases of appendicitis. E. Ruge (*Archiv f. klin. Chir.*, Bd. xciv, Nu. 4, 1911).

Tubercular Typhlitis.—Slow asthenic course, diarrhea, and a higher temperature usually distinguish this disease. The appendix itself may also be the seat of the tuberculous process.

The writer observed 12 cases of acute tuberculous inflammation of the ileocolic glands, with the symptoms those of acute appendicitis. In no case was a palpable tumor present. In some there had been a history of one or more previous attacks of appendicitis. The simulation is so close that a differential diagnosis is almost impossible. The appendix was usually removed, but no tubercle bacilli could be found in it. The infected glands were dissected out. The prognosis is good, only 1 case developing a tuberculous taint. Homer

Gage (Boston Med. and Surg. Jour., Aug. 26, 1915).

About 0.5 per cent. of all appendices removed surgically are tuberculous. The writer had one case in 179 appendices examined. There is an afternoon temperature, progressive weight loss, evening sweats and pain and tenderness in the right lower quadrant. The prognosis is unfavorable except in the very rare primary forms of the disease, but best in the hyperplastic form. J. R. Scott (Annals of Surg., Dec., 1917).

Tumors.—In cancer, the neoplasm which occurs most frequently in the intestines, the subject is usually beyond his 40th year. The progress is slower and the temperature seldom much above normal. Cancer of the appendix, or involvement of the latter have also been observed.

In a young girl of 14½ years, operated upon for acute appendicitis with peritonitis, near the cecal insertion the appendiceal lumen was almost obliterated by a white-yellowish mass about the size of a cherry. It was developed at the expense of the mucosa. Histologic examination showed the tumor to be an atypical epithelioma, the center of it having involved the muscular bed. Two years after removal the patient was found to be in excellent health. E. Kirmisson (Bull. et mém. Soc. de chir. de Paris, xliii, 1432, 1917).

The literature contains reports of over 300 cases of primary carcinoma of the vermiform appendix, according to the writer, although it has never been diagnosed clinically before operation. No symptom or symptom-complex other than that of the ordinary acute or chronic appendix has ever been found. As it may give rise to extension or metastases, every appendix should be subjected to both careful gross and histologic examination. S. P. Reimann (Amer. Jour. Med. Sci., Aug., 1918).

Typhoid Fever.—Perforation occurs late in this disease, while the tempera-

ture, the petechiæ, and other characteristics readily serve to distinguish it. In case of doubt the blood should always be examined for the Widal reaction.

Localization of typhoid infection may occur in the appendix. The diagnosis rests upon the symptomatology of appendicitis proper and that of typhoid, as well as the Widal test. F. Fazio (Gior. Intern. d delle Sci. Med., Dec. 15, 1912).

The writer observed 4 cases of diagnosis of appendicitis in early typhoid fever. In 3, pain, not fever, seemed the symptom which first attracted attention. There was a moderate leucocytosis in all. In none was the Widal reaction positive, but it became so later. In all cases the appendix was congested, but not acutely inflamed, with the large and small intestines hyperemic and the mesenteric and prevertebral lymph-nodes usually greatly enlarged. There is also less rigidity and tenderness in the typhoid cases than in genuine appendicitis. Headache is more common. If the abdomen is not markedly rigid, even though pain and tenderness in the right iliac fossa exist, and if the leucocyte count remains low, operation should be deferred until diagnosis is reached. Winslow (Annals of Surg., Nov., 1915).

Pneumonia and Pleurisy.—In some cases the symptoms closely resemble those of pneumonia or pleurisy. An examination of the lungs will clear up this point. In the former a sudden and persistent rise of temperature may occur.

Disorders of the genitourinary organs, uterus, adnexa, and pelvic cellular tissue, especially salpingitis, are conditions which may cause confusion. Examination of the genitourinary organs sometimes establishes the differential diagnosis, but occasionally complications occur which render it difficult. X-ray examination is of great aid in this connection.

In young women pain and tenderness in the right side, without rigidity, fever or leucocytosis is usually not appendicitis. Apparently severe and long-continued pain in the right side in girls is more likely to be neurotic than appendiceal. Pain may also be reflected from the pelvic organs or other viscera, and the primary seat of trouble may be determined by more careful examination. Winslow (*Jour. Amer. Med. Assoc.*, Feb. 7, 1914).

A fecalith in the appendix as a rule is invisible by the X-ray. But if calcium salts are deposited on it through inflammation it may become demonstrable. A fecalith in the appendix may be mistaken for a ureteral calculus. The passage of an opaque ureteral catheter will usually help in making the diagnosis. Where doubt remains, a Röntgen examination, combined with an opaque meal or an enema, should be made. The writers call attention to the possibility of encountering a left-sided appendix due either to non-rotation of the colon or to complete transposition of the viscera. The former condition was encountered in 3 persons, and the latter in 12. A shadow on the left side may represent a calculus in the appendix unless the X-rays show the cecum to be on the right. Douglas and Lewald (*Jour. Amer. Med. Assoc.*, June 17, 1916).

In making an X-ray diagnosis between ureteral calculi and calculi of the appendix, one should remember that ureteral calculi are situated more internally. An error is possible only when the appendix lies over the psoas and hanging over the brim of the pelvis, and is much elongated. Impacted gall-stones appear at a higher level. G. Vilvandre (*Arch. of Radiol. and Electrotherapy*, July, 1916).

In a clinical study of the relation of appendicitis to intrapelvic disease in women, the writer found that appendicitis in the female could be mistaken for pyosalpinx, ovarian abscess, suppurating ovarian cyst, torsion of the pedicle of an

ovarian cyst, ectopic gestation, abortion and dysmenorrhea. He, therefore, urges the importance of a careful history in each case. A bimanual or recto-abdominal examination should be part of the physical examination of every female patient beyond the age of puberty. Acute pelvic inflammation is usually preceded by vaginal discharge and dysmenorrhea, and appendicitis, by digestive disturbances or previous attacks of pain on the right side. In pyosalpinx the pain is more constant and less severe and is situated lower in the pelvis, the tenderness being frequently most acute over Poupert's ligament. In the other conditions a carefully taken history and physical examination usually make the diagnosis clear. If at the time of operation an incision is made for the exposure of the appendix, the surgeon's finger should always be passed into the right pelvis to palpate the right adnexa. F. C. Hammond (*N. Y. Med. Jour.*, June 5, 1920).

By placing the patient on her left side with the shoulders low and the legs drawn up, it is much more easy to detect the position and condition of the appendix, and also to differentiate it from the uterine adnexa, than by palpation of the patient lying on her back. Even when no great intestinal distention is present, the depth at which the appendix might lie is greater, and the tension of the abdominal walls is likely to be more marked in the dorsal position than when this lateral method is employed, if no intestinal adhesions are present.

The following sign is often useful in the diagnosis between appendiceal and pelvic inflammation: By stretching the skin of the abdomen slightly to increase its translucency, the veins internal to the anterior superior spine, and running upward and slightly inward, will be found darker than elsewhere when the appendix is involved. Skinner (*Jour. Amer. Med. Assoc.*, Feb. 26, 1910).

In appendicitis the pains are more violent, but more strictly localized, and radiating pains are absent. In catarrhal

salpingitis, especially if the ovaries share in the inflammation of the tubes, the pains radiate toward the thigh; the alarming symptoms also show a noticeable remission toward the third or fourth day.

In an acute progressive case of appendicitis, the abdomen is so rigid that deep palpation is difficult and dangerous. A rigid abdomen, according to Robert T. Morris, is the principal differential sign between acute appendicitis and salpingitis.

Four cases of small ovarian tumors with symptoms suggesting appendicitis as the pedicle became twisted. The cause of the trouble was differentiated before operation only in 1 case, and then by pain in urinating. In operating for appendicitis, it is important to examine the genital organs and to have the patient understand beforehand that it may prove necessary to remove some of them. Ranzi (*Berl. klin. Woch.*, Jan. 6, 1908).

According to Deaver, **movable kidney** is to be differentiated as follows: In appendicitis there is more apt to be fever and increased pulse rate, the rigidity of the abdominal wall does not involve such a large area, there is a circumscribed and acutely tender point, the tenderness is more superficial, and there is an absence of a movable tumor which readily slips from between the examiner's fingers.

Infectious catarrhal inflammation of the bile-ducts and ulceration of these ducts may occasionally simulate appendicitis. Biliary colic is to be differentiated by jaundice, absence of fever, peculiar color of the stools, finding of gall-stones in the passage, and by the more severe and continuous pain, radiating usually from the chest margin to the umbilicus. The typical pain in the right shoulder-blade is an important diagnostic sign of gall-bladder disease.

Pain in the lower right quadrant of the abdomen does not always signify appendicitis, but may be associated with hernia, renal or urethral calculus, ovarian incision, appendicitis, etc. Differential diagnosis must be made by a close urinary examination, followed by radiography, and occasionally by urethral examination with a waxed catheter or bougie. In calculus, no matter where situated, the following are the painful areas: the testicle, penis, and inner surface of thigh, as well as McBurney's area. In simple calculus, pain rigidity of the abdominal muscles is not usually present. The relaxation of the pressure is not followed by the pain usually noticed in acute appendicitis. The pain is not usually increased in a line toward the umbilicus, while pain on coughing and deep respiration are unusual. Elevation of temperature is not usually present in calculus cases, save in the presence of an infective process. Pain in the back, loin, groin, inner surface of thigh, urethra, testes, and penis in the male, and in the vulva and urethra in the female, with frequency of urination, definitely points to a possible renal calculus. No better diagnostic means is at our disposal than the X-ray. Erdmann (*Med. Record*, Mar. 14, 1908).

Mistakes in the diagnosis are easily made in cases of appendicitis, owing to its symptoms, which may point to almost any abdominal or pelvic condition. In other cases, such as stone in the ureter or kidney, the symptoms may point to appendicitis and lead to removal of this organ, leaving unremedied the true cause of the trouble. Impacted stone in the right ureter is not infrequent, giving symptoms almost identical with appendicitis, but the X-ray will disclose the real condition. Richardson (*Annals of Surg.*, Feb., 1912).

Among 946 appendicitis cases operated on in Finland, the writer found in 21.6 per cent. a familial predisposition to the disease. A nervous or tuberculous taint was evident in 50 per cent., and only 8.4 per cent. could be classed as robust. Dyspepsia had been noted in 51.6 per cent. of the

destructive and in 58.8 per cent. of the catarrhal cases. Gastroptosis was found in 34.7 per cent. of the severe cases in men and in 79.7 per cent. in the women; in the catarrhal cases, in 55.2 per cent. of the men and 77.7 per cent. of the women. The well-to-do were affected more than the working classes. Chronic constipation was a factor, but there was no connection with acute enteritis or colitis, acute infectious disease, or the seasons. Backman (*Finska Lakare. Handl.*, lviii, No. 6, 1916).

Simple empyema of the gall-bladder is diagnosed by the onset, the location and character of the pain and tenderness, and by the area and degree of rigidity.

Acute phlegmonous cholecystitis and gangrene of the gall-bladder may usually be diagnosticated by the existence of more acute symptoms, more general peritonitis, by the rapid and shallow respiration, location of the pain and tenderness, and by the greater tendency to a rapidly fatal issue.

Perforated gastrointestinal ulcers are diagnosticated by predisposing age, history of previous gastric or intestinal disturbances, sudden acute pain in the epigastrium, followed by collapse, and last by the presence of bloody vomiting, or, in the case of intestinal ulcers, by the hemorrhage from the bowel. Perforation occurring in typhoid may be very difficult to tell from a concurrent appendicitis.

Extra-uterine pregnancy is to be recognized by the existence of the usual subjective signs of pregnancy, by vaginal examination, and by the absence of inflammatory symptoms prior to the rupture.

ETIOLOGY.—Young adults under the 30th year, especially males, constitute the majority of cases. Appendicitis occurs at all ages, however, and is not

uncommon in the first two years of life. It is more common during the first six months of the first year and the last six months of the second year.

In 200 appendices of children examined by the writer, 15 showed inflammatory changes of varying intensity. The two youngest infants were 13 and 17 days old, respectively. In nine instances the age ranged between 20 and 30 days. Four infants were between 1 month and 2 months old. In two instances the cecum was still in an incompletely descended position, lying between the iliac crest and the liver; but in the remainder of the cases the cecum occupied its usual position in the iliac fossa. Three times the distal part of the appendix was found hanging over the pelvic brim, and in such instances the distal part gave the evidence of severe inflammation. In 8 cases the appendix occupied a position directly behind the cecum and proximal part of the ascending colon. It is in this position of the appendix that in infants sharp angulation frequently occurs. Smith (*Amer. Jour. of Dis. of Children*, April, 1911).

The writer observed 29 cases of appendicitis in patients between the ages of 51 and 72 years. In only 15 were the symptoms typical. In 4 cases the insidious onset, with emaciation and signs of intestinal obstruction in 3 cases, and even blood-stained stools in 1 instance, suggested cancer of the large bowel, but the trouble subsided after removal of the chronically inflamed appendix. In another case the only symptoms were from the stomach: emaciation, tenderness in epigastrium, hyperacidity and lactic acid, and doubtful X-ray findings pointed to gastric cancer, but all symptoms ceased after appendectomy, the chronic appendicitis having caused adhesions between the ascending colon and duodenum. J. Philipowicz (*Wiener klin. Woch.*, Dec. 25, 1913).

Appendicitis was found more frequently in the army than in civil life. This is probably due to fatigue and exposure to wet and cold, which ren-

ders a latent infection acute by lowering the resistance or it may even give origin to primary acute appendicitis. The crises are particularly severe but men who are inured to hardships endure these crises often without seeking aid, and such cases arrive at hospitals with fully established diffuse peritonitis and perforated appendices.

When the diagnosis of appendicitis is made, the patient should at once be sent to a surgical center where he can be operated upon if necessary. Rouchier (*Bull. et mém. Soc. de chir. de Paris*, xliii, 1846, 1917).

In all of 131 cases, excepting 1, operated on by the writer as soon as seen, there were 89 of acute appendicular obstruction, of which 10 showed obstruction only, 18 showed obstruction with a varying amount of gangrene of the wall, and in 59 rupture of the appendix had followed the gangrene. In the obstructive cases the writer holds that the primary cause of the disease is obstruction of the lumen of the appendix. On examination of the appendices removed at operation it was found that obstruction had been due to one of 5 causes: (1) concretions (50 cases); (2) strictures (6 cases); (3) kinks (rare); (4) bands; (5) worms, fruit seeds, and other foreign bodies. S. T. Irwin (*Lancet*, Jan. 18, 1919).

The conformation of the organ also influences markedly the development of the disease. Its length may vary from a fraction of an inch to 12 inches. It may also point in any direction, though in most instances downward and inward. It is sometimes connected with the ovary by a ligament. Forming, as it does, a more or less long, blind sac, which opens into the cecum, it is more or less exposed, according to the size of its aperture and the direction of the latter to the penetration of fecal matter, any foreign body the latter may contain, and to kinks, tumors, adhesions,

etc., which compress it or obliterate its lumen.

Insufficient attention has been given to ectopic appendices. Apart from cases of misplaced appendix and those in which it may have become displaced through inflammation, we may have: (1) An appendix, normal, with adequate mesentery, free in the iliac fossa, in front of, behind, or beside the cecum; (2) ectopic appendix, situated too high, with or without retention of the cecum, and drawn up by a too short mesocolon; (3) a dystopic appendix, by abnormal descent of the cecoappendicular portion toward the pelvis or the umbilical region. These abnormalities give rise to symptoms of colic, owing simply to their position, and without any accompanying inflammation. Lerda (*Presse méd.*, Jan. 13, 1912).

While the entire sac is lined with lymphoid tissue, an accumulation of the latter at the orifice forms what has been termed Gerlach's valve. Its functions are not known.

Various diseases favor the development of appendicitis: gastrointestinal disorders, influenza, typhoid fever, and particularly constipation and cold. The local inflammation may be caused by the intrusion of: micro-organisms, specific and non-specific; constipation, dietetic indiscretions, and the habitual use of meat. Fatty compounds of saturated fat have recently been urged as etiological factors. The rarity of appendicitis in the Chinese appears according to Matignon to confirm the opinion of Keen and Lucas-Championnière as to the predisposing influence of meat diet, meat in China being a luxury within the reach of few.

Appendicitis has a markedly different incidence in various countries, and this different incidence may be largely a question of diet. Statistics show that, where there is a large meat-eating population, appendicitis is a common

disease, whereas in those countries where little meat is eaten appendicitis is rare if not almost unknown. Williams (Brit. Med. Jour., Dec. 31, 1910).

Williams believes that appendiceal concretions are made up of compounds of saturated fatty acids the origin of which is excess in secretion or defect in absorption of calcium and fatty acids. A large increase of calcium soaps is found in the submucosa and mucosa of some appendices, in certain cases producing marked thickening. Thus, by cutting off the nutritive supply, bacterial invasion is facilitated. Anthony (Jour. Med. Research, vol. xxv, p. 359, 1911) studied 48 cases in which various fat stains to differentiate fatty acids and calcium soaps were used. While neutral fats and slight amounts of fatty acids occur in control cases, in acute and chronic appendicitis fatty acids and calcium soaps predominate, and seem to increase with the age of the patient, especially between the ages of 25 and 50 years. This, in general, confirms Williams's views. (Amer. Jour. Med. Sci., April, 1912.)

Of late, tonsillitis and pus laden tonsillar crypts, parotitis and streptococcic disorders of the teeth have been incriminated.

Case of appendicitis in which inflammation of 1 of the tonsils co-existed. From the appendix fluid and from the tonsil the writers isolated the same organism, a streptodiplococcus. This organism induced arthritis in rabbits, and in one caused an acute appendicitis. In the appendix the diplococci were found in the mucous and submucous membranes, though far more numerous in the serosa. Poynton and Paine (Lancet, Aug. 17, 1912).

In appendicitis following acute tonsillitis, the appendicular involvement may be only part of a generalized infection; hence the gravity of such cases is out of proportion to the local symptoms. They are apt to be atypical in course, and after smouldering to suddenly develop fulminat-

ing symptoms. Chronic tonsillar infections should likewise be borne in mind as the possible cause of appendix infections. Anderson (Amer. Jour. Med. Sci., Oct., 1915).

The clinical relationship of appendicitis and tonsillitis does not depend for its acceptance on the theory of a hematogenous origin. Chastenot produced appendicitis in rabbits by feeding pathogenic bacteria; the possibility of infection from the tonsil by way of the alimentary tract is, therefore, apparent. S. C. McCoy (Lancet-Clinic, July 15, 1916).

The writers report 8 cases of acute appendicitis developing within 12 days in conjunction with 34 cases of parotiditis within 3 months. Several appendices were examined bacteriologically and all showed streptococci, some in almost pure growth. Streptococci were found in milk used by these patients and these germs when inoculated into rabbits, caused appendicitis in some and parotiditis in other animals. Rosenow and Dunlap (Jour. of Infect. Dis., Apr., 1916).

Case of appendiceal abscess in which the infection probably came from the roots of the teeth, the culture from the pus evacuated from the peritoneal cavity having been pure culture of *streptococcus viridans*. Markoe (Bull. Lying-In Hosp., City of N. Y., May, 1917).

Rosenow demonstrated the fact that the streptococcus group has an elective affinity for certain tissues. He was able to produce appendicitis in 68 per cent. of animals inoculated with cultures of streptococcus isolated from cases of appendicitis, while only 5 per cent. of the animals were so infected by cultures of streptococci isolated from widely varying sources. The writer adduces data which tend to prove that acute appendicitis is an acute metastatic focal infection in many instances. Out of 236 cases, 214, or 91 per cent., were primary attacks; 22, or 9 per cent., were recurrent. Of the 214 cases, in 183, or 86 per cent., there were definite primary infections of the upper

respiratory tract. There was no such evidence in 31, or 14 per cent. The respiratory infection preceded the appendiceal attack on an average of sixteen days, the extremes being one and sixty days. The appendicitis most usually followed the subsidence of the constitutional symptoms accompanying the nasal or throat infections. J. S. Evans (Wisc. Med. Jour., xvii, 91, 1918).

Neighboring catarrhal, pelvic, typhoid, and tubercular processes; constriction, torsion, or strain have also been enumerated.

The association of appendicular and pelvic disease is due to contiguity rather than to continuity of structure. The accidental inward direction or pelvic position of the appendix is the chief factor in this association. The appendix or the pelvic organs may provide the primary source of disease. Appendicitis is a frequent source of dysmenorrhea and its associated mucous colitis. The association of appendicitis with pelvic disease is the exception, and not the rule. The appendix is not a vestigial structure, but a highly differentiated portion of the intestinal tract, and plays an important part in intestinal digestion. The systematic removal of the appendix during laparotomy for pelvic disease in the absence of evident disease is not justifiable. Helme (Brit. Med. Jour., Dec. 15, 1906).

The frequency of adhesions of the cecum, sigmoid, and appendix after gynecological laparotomies were studied by the writer. Among 160 cases, the appendix was free of adhesions in only 70 cases, the cecum in 36, and the sigmoid in 20. Congenital peritoneal adhesions did not appear in more than 20 per cent. of the cases. Microscopic examination of 100 appendices revealed that of 99 appendices only 20 were normal, 43 showing signs of old changes, mild in degree, and 31 signs of severe phlegmonous or ulcerous processes, although the history showed no previous attack of appendicitis. Diseases of the appendix are usually

secondary to disease of the colon. The transmission takes place by infectious intestinal contents penetrating the appendix and being held there for some time. Opitz (Deut. Gesellsch. f. Chir., 1914; Surg., Gynec. and Obstet., May, 1915).

Following 896 laparotomies for gynecologic disease, concomitant appendix disease present in 16.4 per cent., was found to be secondary to the gynecologic lesion in most instances. Lesions were found in the appendix in 75 per cent. of the cases of torsion of a cyst in the right ovary, and in 23.7 per cent. of the cases of right tube or ovary disease, but never with left tube or ovary disease alone. While simple congestion in the appendix with gynecologic disease does not alone warrant appendicectomy, systematic investigation of the right tubes and ovaries as a routine measure in all cases of appendicitis should always be carried out. Waegeli (Corresp. bl. f. schweizer Aerzte, Aug. 24, 1918).

The writer describes 11 cases of torsion of appendices epiploicae which had been under observation in the Mayo Clinic in the past 10 years. Seven of these cases were true torsion of the appendix epiploica; one was of doubtful torsion, acting as a band producing intestinal obstruction; two of incarceration in a left inguinal hernia, and one of a foreign body in the peritoneal cavity with unproved origin from an appendix epiploica. Four of the cases of torsion presented acute symptoms, for which operation was done, and in the remaining 3 cases the torsion was probably symptomless, as it was found in the course of abdominal operations for other pathologic conditions. Hunt (Annals of Surg., Jan., 1919).

Cases due to actinomycosis and other parasites are occasionally observed. Appendicitis may be caused by ova of the *Ascaris lumbricoides* and *Trichocephalus dispar*. The removed appendix has also been found to contain ova

of *Bilharzia hematobia*. The stools should, therefore, be examined for worms or their ova.

Case of appendicitis in a child in which the appendix after removal was found to contain a nest of actively moving thread-worms. H. A. Lediard (Lancet, Sept. 17, 1910).

Study of 129 cases of appendicitis in children in 19 of whom the appendix contained the oxyuris or the trichocephalus, the former parasite seventeen times, the latter twice. In 15 of the 19 cases the parasites were associated with a non-suppurative catarrhal type of appendicitis; in the 4 remaining cases the appendix was gangrenous. These parasites, when present in a diseased appendix, are in most cases the exciting cause of the pathological changes found. Cecil and Bulkley (Jour. of Exper. Med., March, 1912).

The pinworm is a comparatively common cause of appendicitis. Reporting 13 cases of appendicitis in persons harboring the oxyuris (pinworm), the writer concludes that chronic discomfort in the appendix region in adults, especially sharp pains, increasing during exercise, should suggest the possibility of oxyuris infection. Even without signs of the parasite in the stool, a course of treatment for *Helminthiasis* should be given, to be stopped at once if signs of acute febrile appendicitis develop. Rheindorf (Med. Klinik, Apr. 20, 1913).

Traumatism, blows upon the abdomen, etc., sometimes produce inflammation of the appendix, probably, however, only when the organ has already been the seat of some lesion or so disposed anatomically as to receive the blow directly.

A study of 1400 cases showed that trauma was never the direct exciting cause of acute appendicitis in a perfectly normal appendix. An acute attack of appendicitis can follow a severe blow upon the abdomen or fall thereon, or

may be the result of muscular contractions of the ileopsoas muscle in an appendix which has been previously inflamed only under the following conditions: In a latent or residual abscess or extensive pathological lesion of the appendix, where the appendix did not occupy a deep pelvic position, but is in close proximity to the anterior abdominal wall, severe direct traumatism may precipitate an acute attack. Strong contractions of the ileopsoas muscle cannot be the immediate cause of an acute attack of appendicitis, where the appendix is chronically diseased or where it has extensive pathological lesions, unless it is firmly adherent, and not simply in apposition, to the peritoneum overlying this muscle. The degree of traumatism to be a factor in the causation of appendicitis must be direct and of considerable force. Such force, applied to the right iliac fossa, may tear the underlying parietal peritoneum and so simulate an acute attack of appendicitis that only opening the abdomen and exposing the appendix could definitely settle the matter.

The mortality is very high in these cases on account of (a) the failure to recognize the condition until the disease is well advanced; (b) the rapid gangrene and perforation which occurs, and (c) the delay in operation. The writer urges a more careful study of this class of cases and, as soon as a diagnosis has been made, an immediate operation—if the best results are to be obtained. J. B. Deaver (New York Med. Jour., June 15, 1907).

The appendix, by virtue of its position and structure and the history of its inflammation, is susceptible to traumatism; it sometimes is traumatized, and its inflammation sometimes follows such injury. There is every reason, therefore, to regard traumatism as an etiological factor in appendicitis. J. P. Warbasse (N. Y. State Jour. of Med., Aug., 1908).

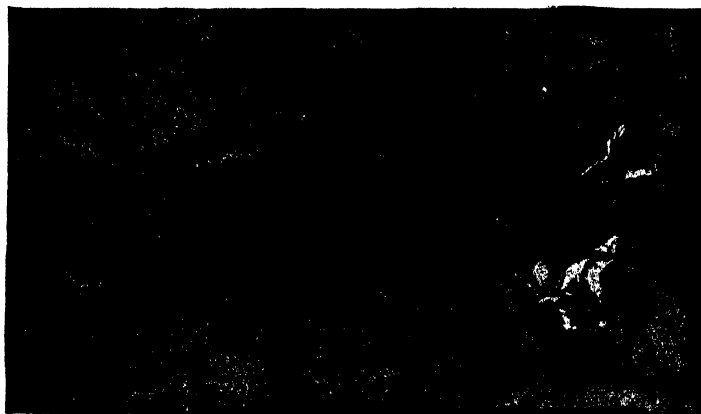
Case which strongly supports the view that appendicitis is caused by traumatism. A man heard a wagon coming behind him, turned sharply, and at the same time sprang to one side. He was

immediately seized with severe pain in the region of the cecum, was operated upon within a short time, and the appendix found to be torn in two with the fragments widely separated. Vogel (*Munch. med. Woch.*, June 9, 1909).

Two personal cases appeared, before operation, to be clean-cut appendicitis of a traumatic etiology. One supervened twenty hours and the other thirty-six hours after a kick from a horse. Both were operated on radically at once. The first was found to be a rupture of the intestine with perforation near the cecum re-

through deficient actions of a valve which usually closes its opening, or on account of excessive patency of the latter.

Kelly states that in 1000 cases operated upon in Johns Hopkins Hospital in only four instances were foreign bodies found. He quotes 2527 cases with but 10 due to the presence of foreign bodies—only $\frac{2}{100}$ of 1 per cent. of the entire number. Murphy found foreign bodies present in 3.5 per cent. of his cases, while Fitz and Matterstock found them in 12 per cent. of



Appendix containing hardened fecal masses. (J. F. Pilcher.) (*New York Medical Record*.)

quiring extensive resection. The second case suggested the same diagnosis—abdominal contusion from a horse-kick with possibility of traumatic appendicitis; but the patient was found to have typical appendicitis, due to a fecal concrement with beginning peritonitis. There were no anatomical alterations which could be set down to trauma. On the whole, these cases are mere coincidences of appendicitis with another lesion. Sprengel (*Deut. med. Woch.*, Dec. 14, 1911).

Irritating fecal matter, which frequently forms hard, egg-like fecal concretions of various sizes; foreign bodies—cherry stones, orange seeds, buttons, spicules of bone, pins, etc.—which penetrate into the interior of the appendix

their perforative cases. Ranvier discovered 16 foreign bodies in 439 post-mortem examinations, or 3.5 per cent. of the cases. It is probable that all cases, perforative and non-perforative, will show but from 2 to 3 per cent. as due to the irritation and actual trauma induced by the presence of foreign bodies. To this may be added the slightly larger percentage arising from the presence of fecal concretions (stercoral appendicitis). When these cases are included, it will be found that about 12 per cent. of the patients operated upon may be grouped under the so-called traumatic class. J. D. Robertson (*Surg., Gynec., and Obstet.*, Oct., 1911).

Foreign bodies are present in the appendix in about $2\frac{1}{2}$ per cent. of operated cases. More than 52 per cent. of them *pins*. The habit in in-

fancy and childhood of placing everything in the mouth seems responsible for about one-third of the pin cases, but a history of having swallowed the pin is rarely elicited. R. H. Fowler (Long Island Med. Jour., Dec., 1914).

In 400 operations on the appendix the writer found a foreign body in 10 cases. In 6 there was a living oxyuris, 4 of these patients being girls between 6 and 17; in others a hair, part

A personal analysis of 1000 cases showed that in a large percentage of cases there was a short mesoappendix, causing fixation of the proximal portion of the appendix and leaving the distal part free. This tended to cause the appendix to fold on itself and interfered with the circulation. Then there is the retroperitoneal appendix, and the appendix in which there is no sharp demarcation between the end



Section of appendix containing hardened fecal masses. (J. F. Pitcher.) (New York Medical Record.)

of the head of an oat, a sliver of wood, a grapeseed, a blackberry stone or small shot. Grondahl (Norsk Mag. f. Laegevidenskaben, Dec., 1915).

Grape seeds were at one time thought to play an important rôle as etiological factors, but a painstaking investigation by Edmund Andrews showed that this was not based on facts. Indeed, it is quite probable that foreign bodies play a very small part in the production of attacks of appendicitis, excepting hardened fecal masses.

of the cecum and the beginning of the appendix. Appendiceal concretions play a small rôle and so, too, thrombosis of the artery of the appendix. Infection of the mucosa, inflammation of neighboring organs, traumatism, and some unusual gastronomic feat were noted as causes of appendicitis. In 4 cases the passage of a renal calculus operated as a cause, while in 1 case a gall-stone was found in the appendix, although foreign bodies played almost the least important rôle of the various factors. G. Crile (Ohio State Med. Jour., June, 1907).

PATHOLOGY.—The vermiform appendix is a glandular organ presenting a certain analogy to the tonsils and liable, as well, to follicular, mucous, submucous, infectious, exudative, and ulcerative disorders.

Examination of 1500 specimens led the writer to conclude that there is no pathological evidence that an acute catarrhal appendicitis occurs, nor is there evidence of "involution" nor of "chronic catarrhal" inflammation of the appendix. The only justifiable classification of inflammation of the appendix is: (1) Acute appendicitis; (2) healing or subacute appendicitis; (3) healed or chronic appendicitis. Acute localized peritonitis is always present in acute appendicitis as early as 12 hours after the onset; the absence grossly of a localized peritonitis in suspected cases is *ipso facto* evidence of absence of acute appendicitis. In addition to obliteration and stricture, attention is called to 2 new, constant and pathognomonic signs of chronic appendicitis, namely: (1) absence of mucosal crypts, and (2) marked widening of the submucous connective tissue zone. The latter is especially easy to determine in cross sections. Moschowitz (Annals of Surg., June, 1916).

An appendicular inflammatory process is usually started by the *Bacillus coli communis*. In a certain proportion of cases other micro-organisms, especially the *Staphylococcus pyogenes* and streptococcus, are also found.

The writer made cultures from the appendix in 14 cases of acute appendicitis and 6 of chronic. Streptococci, usually in predominating numbers, were isolated from the tissues of the appendix in 17 cases. The colon bacillus was found in pure cultures in the pus within the lumen in 6 cases and with streptococci or other organisms in the rest. The cultures from the wall, after thorough washing, showed that here the chief bacteria were

streptococci. The fusiform bacillus was isolated from the wall of the appendix in 3 cases. Other anaërobic bacilli and spirilla were found in some cases; the bacillus welchii in 2; a diphtheroid bacillus in 2; the staphylococcus aureus in 1; the bacillus pyocyaneus in 1, and unidentified cocci and bacilli in 2. Rosenow (Jour. of Infect. Dis., Mar., 1915).

The writer injected staphylococci into the blood of rabbits, he found



Section of appendix showing areas of obliteration and necrosis. (J. F. Pilcher.) (New York Medical Record.)

that the normal appendix proved able to eliminate the bacteria derived from the blood, passing them into the intestines without harm if the appendix was permeable. But if it was obstructed, the staphylococci from the blood soon set up inflammation in it, with complicating peritonitis. Mordvinkin (Roussky Vratch, May 21, 1916).

In 30 per cent. of the cases of acute appendicitis seen at the beginning of the attack by the writer, the

mucosa of the appendix was found destroyed during the first day, and in 70 per cent. after the second day of the attack. Due to loss of this protective barrier the wall of the appendix is invaded by the putrefactive bacteria. Gangrene developed on the second day in 46 per cent. of the cases, on the third day in 53 per cent., and on the fourth day in 65 per cent. A purulent peritoneal exudate was found in 18 per cent. on the second day and in more than 40 per cent. on the third and fourth days. He observed that a leucocytosis of 20,000 tended to confirm the diagnosis. The course was generally determined during the first 2 days and it is only during this short interval that expectant treatment may be employed as a means of arriving at a diagnosis. After this period, temporizing may be fatal. E. Kummer (Rev. méd. de la Suisse Rom., xl, 133, 1920).

Various forms of appendicitis have been described, but these are in reality stages of the fully developed morbid process. The mildest, or *simple catarrhal*, form is usually caused by constipation or an indiscretion in diet, in which the inflammatory process, after passing through an acute stage, including more or less epithelial desquamation, excoriation, etc., and involving the mucosa, submucosa, and the serous layer and the overlying area of peritoneum, gradually recedes. The appendix remains very vascular and functionally weakened, and is subject to renewed attacks of inflammation.

Microscopic examination of 539 appendices removed during or within 10 days after an acute attack, together with the gross pathology in over 500 cases by the writer, showed that during the first 24 hours of an attack the pathological changes are similar in nearly all cases, a definite obstruction of the lumen of the appendix being always present, distally to which the organ is distended. Following on the first 8 or 10 hours,

fibrin is found on the peritoneal surface, and toward the close of the first twenty-four hours a considerable proportion of the appendices show commencing gangrene macroscopically. Surgically, the peritoneal involvement of the first day may be ignored and the abdomen closed without drainage. On the second day, owing to coalescence of microscopic necrotic areas, macroscopic areas of gangrene are noticeable, and perforation, if it is going to occur, usually takes place on this day. In the majority of cases there is now a definite fibrino-purulent exudate on the peritoneal surface. By the third day destruction has usually reached its maximum, evidence of commencing repair now appearing in the presence of fibroblasts in all sections. On the fifth day in the non-gangrenous cases, the polynuclear leucocytes have almost disappeared. Protection of the peritoneal cavity in appendicitis depends upon maintenance of the fibrous periappendicular adhesions rather than upon the bacterial impermeability of the appendicular walls. The writer agrees with Deaver, Moynihan, Ochsner and others that clinical perforation would almost never occur if the practitioner and laity would appreciate that in appendicitis "perforation spells purgation" and withhold cathartics during the early stages of suspected cases. Stanton (Amer. Jour. Med. Sci., Apr., 1915).

The writer recognizes 4 types of appendicitis. The first, the most common, is that of fibroid degeneration in the walls of the appendix. This is not an infectious process but rather an irritative one, due to the contraction of the hyperplastic connective-tissue upon the nerve-endings in the appendix. The next most common form is the acute intrinsic infective type. The third is the extrinsic infective type, the complement of extensive infection in the neighborhood, such as pyosalpinx or ovarian abscess. The fourth type the writer adds is the syncongestive form. Appendix symptoms in such

instances are probably due to the fact that the soft inner coats of the appendix find difficulty in swelling within the light outer sheath. R. T. Morris (Med. and Surg., i, 91, 1917).

The *ulcerative*, or *perforative*, variety gives rise to many complications, abscesses in other, even remote, structures, as will be shown presently (p. 106). In this form the inflammation is often initiated by fecal concretions or foreign bodies, and gradually proceeds to ulceration. An opening is created by the ulceration, and the fecal concretion or foreign body escapes, with the septic discharges formed, into the abdominal cavity. Often, however, the perforation is at a point other than that occupied by the fecal concretion.

The writer classifies appendicular abscesses as follows: (1) in front of, below, and outside of the cecum, the pus being confined by the cecum, small bowel, omentum, etc.; (2) outside the cecum and ascending colon or behind the cecum in the layers of the mesocolon; (3) in the pelvis; (4) near the median line to the median side of the cecum; (5) free in the abdominal cavity or in many pockets between the coils of intestines. In addition there are seen secondary abscesses close to the original abscess, residual abscesses at the site of the primary abscess; and metastatic abscesses at any distal point or as a parotid abscess, pyelephlebitis, etc., Deaver (N. Y. Med. Jour., Feb. 5, 1916).

In 146 cases collected by Matterstock perforation was found to have occurred 132 times. Properly treated, however, every case of appendicitis should be operated upon before perforation has occurred. Ulcerative appendicitis may also occur in the course of an infectious disease, especially typhoid fever.

If, however, through previous local inflammation, close adhesions have

united the appendix and the parietal peritoneum, the appendiceal contents may pass entirely through the peritoneal coats. This gives rise to an extraperitoneal abscess, which may open externally above Poupart's ligament or within the abdomen into the small intestine, the bladder, the vagina or the rectum, the portal vein, the iliac artery, etc.

Pleurisy, to which reference has already been made, is due to propagation of the pyogenic process through the retroperitoneal cellular tissue, or through the lymphatic system. It often passes unperceived, is almost invariably on the right side, and is rarely bilateral.

If there are no adhesions between the appendix and the parietal peritoneum suppurative peritonitis is produced, and this process usually gives rise to a protective plastic exudation, which causes the surrounding loops of small intestine to adhere together and inclose the secondary abscess, thus temporarily protecting the surrounding parts.

If, however, the plastic inflammation does not induce protective adhesion between the intestinal loops, the septic material invades the whole peritoneal cavity, and gives rise to diffuse, and often fatal, peritonitis.

Until the present the so-called "muscular defense" is the only generally recognized early symptom of perforation. The appearance of the tongue, in connection with the general condition of the patient, will give an important suggestion for the early recognition of the disease. Kron (Archiv f. klin. Chir., Bd. xcii, S. 1105, 1910).

Appendicitis in the female is less likely to lead to general peritonitis than in the male, but if chronic and recurrent, is very prone to lead to damage to the female pelvic organs, varying from slight chronic pelvic peritonitis to cystic degeneration of the ovaries, fibrous closure of the

Fallopian tubes, or general pelvic adhesions with all their symptoms and discomforts, including absolute sterility. The physician should urge removal of the appendix in every young woman when there is any inflammation of it, preferably during a quiescent interval. C. E. Cantrell (Pan-Amer. Surg. and Med. Jour., Feb., 1915).

When, as occasionally happens, the abscess rids itself of its contents, pus, blood, feces, detritus, etc., into the cecum, the acute process ceases, the patient proceeding either to recovery or lapses into *chronic appendicitis*, with its chain of recurrent attacks. The appendix may also be the seat of areas of fibrosis, causing strictures, etc., sufficient in some instances to obliterate completely (*obliterating appendicitis*) its cavity. Or, the stricture may block off a point of the latter, and the distal cavity become the seat of an accumulation of thick fluid or mucous (*appendiceal mucocoele*).

Report of 6 cases of self-healed appendicitis discovered during operations for utero-ovarian conditions. In some of these there was no history pointing to appendicitis. In 2 hardly any appendix remained (auto-amputation); in 2 others it was adherent to the abdominal or pelvic wall, no longer inflamed, and sealed up by the peritoneal inflammation around it. In the remaining 2 cases no trace of an appendix could be found, though there were scars in the cecum at the point of insertion. A gangrenous appendix had evidently sloughed and been slowly absorbed. Deppe (Münch. med. Woch., Dec. 3, 1912).

The most threatening complication, *gangrenous appendicitis*, may occur as a complication of either of the above conditions or of arrest by kinking, thrombosis, pressure upon, or any other obstructive agency of the supply of

arterial blood to the organ. In most instances of gangrene, especially when the appendix is found moist green or black, greatly swollen and soft, or even detached from the cecum, an overwhelming local infection is probably the initial factor. Fortunately, where the inflammatory process reaches beyond the appendix proper, adhesions are apt to form around the diseased organ. These adhesions afford protection to the surrounding structures by the time perforation or gangrene occurs. The gangrenous areas are well shown in the annexed colored plate published with an article on the acute form by the late Professor Kocher, of Berne.

In a series of cases of appendicitis in children, 9 per cent. occurred in the first 5 years of life, 54 per cent. between 5 and 10 years, and 37 per cent. between 10 and 15. The important feature of appendicitis in children is early gangrene. A third of the cases were gangrenous throughout or in part and perforation accounted for the peritonitis in another large group. Only one-third of the cases were uncomplicated acute inflammations permitting closure of the wound without drainage. The appendix was retrocecal in 30 per cent. Several times a half twist of the meso-appendix was found, probably a factor in the stasis causing gangrene. Twice there was definite history of trauma. Fecal concretions were found in a fifth of the cases; pinworms, in 3 cases. Comparison of results of operation in adults and children showed the better figures for the children. The author's mortality was less than 4 per cent. in children. M. B. Clopton (Pediatrics, xxvii, 271, 1915).

The abscess does not always open inwardly, *i.e.*, into a neighboring intestinal cavity or the peritoneum; it may open through the abdominal wall.



Acute Gangrenous Appendicitis. (*Kocher.*)

Correspondenz-Blatt für Schweizer Aerzte.

PROGNOSIS.—Death may occur very early, especially in children, who are also more liable to peritonitis than adults. The danger of death is greater in men than in women.

The actual cause of death in many of the fatal cases of appendicitis is due not necessarily to the appendicitis itself, but to some more or less remote complication or secondary condition. In the writer's 300 operative cases there had been 16 deaths from all causes, or 5.3 per cent. No bad case was refused operation. The writer divides the cases into 4 classes: Class I. Appendix acutely inflamed or gangrenous, but with no pus outside the appendix, 59 cases, with 3 deaths. Class II. Acute cases with localized abscess, 64 cases, with 2 deaths. Class III. Acute cases with free pus, 20 cases, with 9 deaths. Class IV. Chronic or recurrent cases, 157 cases, with 2 deaths. The fatal cases he divided into 4 groups as follows: Group I. Recovery from operation and death later from pulmonary embolism, 2 cases. Group II. Death due to accidents and previous diseases, 2 cases. Group III. Cases making good recovery from operation and ending fatally afterward from pulmonary infections, 3 cases. Group IV. Cases making a good operative recovery, but ending fatally some time later on account of exhaustion due to fecal fistula, 3 cases. Group V. Cases ending fatally with immediately continuing symptoms of abdominal sepsis, 6 cases. These last 6 cases are the only ones out of the 16 reviewed which terminated fatally from the immediate effects of the disease. Pulmonary embolism usually occurs about the tenth day and in patients who have apparently been making a good recovery, and is usually secondary to unsuspected local thromboses, very often of the pelvic and lower abdominal veins. Femoral phlebitis, usually of the left side, has been noted in several cases, but all ended in recovery. These cases of

vascular disturbance nearly all occurred in cases without pus and where there was primary union of the wound. Inflammatory conditions in the chest, usually of the right side, are fairly frequent, and nearly always occur after pus cases, especially where there has been general peritonitis. Undoubtedly the anesthetic is partly responsible by impairing the resisting power of the lung. "The Murphy treatment" no doubt results in a lower mortality in pus cases than where more elaborate measures to get rid of the pus are tried, i.e., suction or irrigation. Wainwright (Surg., Gynec. and Obstet., Nov., 1911).

The following conclusions regarding the prognosis of acute appendicitis are now accepted by most surgeons: (1) The mortality in cases operated upon during the first 24 to 36 hours is almost *nil*. (2) Cases without peritoneal involvement localized to the immediate vicinity of the appendix can be operated safely at any period of the attack by a competent surgeon. (3) In cases with early peritonitis of greater or less extent the mortality rises rapidly in cases operated upon after the first day of the peritoneal involvement. (4) Late abscess cases should not be over 5 or 6 per cent. (5) The bulk of the operative mortality today occurs in the severe cases operated in the intermediate stage of the attack, when there is well-marked peritoneal infection of more than 24 hours' duration. E. M. Stanton (N. Y. Med. Jour., Sept. 26, 1914).

In 822 cases at the Cook County Hospital, general peritonitis still proved the most frequent complication of acute appendicitis. In some cases this complication seemed to have been dependent on the too early removal of the drain in abscess cases. Early operation means low mortality. Abscess formation may be considered as evidence of resisting power on the part of the organism. There was a 2.2 per cent. mortality in abscess cases against a 5.5 per cent. mortality

in gangrenous cases without abscess formation. More (*Jour. Amer. Med. Assoc.*, Mar. 24, 1917):

In a study of the statistical reports of several large hospitals in Greater New York, the writer found the mortality of appendicitis to be about 16 per cent. Deaths were principally due to general peritonitis, suppurative peritonitis, and a moribund condition on admission. He condemns the prolonged use of the ice-bag, and regards intestinal fistula one of dangerous sequelae. The cause most potent in the production of these fistulae is neglect of the rule to operate as soon as the diagnosis of acute infective appendicitis is made if the disease is progressive. He formulates the following dicta: In so-called fulminating and late cases study well the pathology of the caput coli and the adjacent tissues about the appendiceal base. If bacteria have necrosed the tissues about the appendiceal base, excise the stump and treat the rent as in gastric ulcer, placing a Mikulicz drain over the Lembert sutures, provided the patient's condition will permit the work. In obstinate fecal fistula following appendicitis, particularly when producing an artificial anus, not only rendering patients helpless, but endangering their lives, resect the cecum and anastomose the small intestine laterally with the cecum. As a large proportion of fecal fistulae following appendicitis close spontaneously, unless of the dangerous variety requiring immediate attention, one should wait from 3 to 5 months for this spontaneous cure. J. C. Kennedy (*L. I. Med. Jour.*, Jan., 1921).

Improved methods of treatment of acute appendicitis, especially every operation as soon as the diagnosis has been made, have brought the mortality down from 30 per cent. to 2 or 3 per cent. Some operators, notably Murphy, claim as low as $2\frac{1}{2}$ per cent.; others even less: 1 per cent. when early operation can be resorted to. A local abscess raises this to an

average of 8 per cent., and, where peritonitis has developed, considerably higher: from 5 to 25 per cent. according to various statistics.

An investigation of the mortality by writing to all of the hospitals in the United States having a capacity of more than 50 beds brought nearly 300 reports; of these, 179 had the reports so classified that accurate figures could be formulated. In all there was a total of 13,445 cases. The total mortality was 7.4 per cent. The hospitals having the largest number of cases (with an average of 13 to each member of the surgical staff) gave the lowest mortality, while the mortality rate in the smaller hospitals was nearly doubled, in the smallest group of hospitals reaching the proportion of 13.7, which approximates the mortality of untreated appendicitis.

As to the mortality of surgeons using the Ochsner treatment, Ochsner and the Mayo brothers, with a combined operation list of 1940 cases, show a mortality of about 2 per cent., while Deaver and Richardson, who believe in operating at once on every case of appendicitis, have an operative mortality of 5 per cent. The surprising results reached by the Mayo brothers in 1894, with 536 operations and a mortality of only 5 (less than 1 per cent.), were reached by applying strictly the rest and starvation treatment in certain acute cases of appendicitis. A possible explanation of these figures may be found in the fact that more interval cases are sent to Mayo brothers than to other surgeons. There has been a marked reduction in the death rate of appendicitis since the advent of efficient surgical measures. Coffey (*N. Y. Med. Jour.*, Aug. 18, 1906).

Series of 100 consecutive operations for appendicitis. The cases, 45 in number, operated upon within four days yielded no mortality as contrasted with a mortality of 20 per cent. for the fifth day, $33\frac{1}{3}$ per cent. for the sixth day, 20 per cent. for the seventh day, 14 per cent. for the second week, and 8 per cent. for the third week. These

45 cases included examples of each of the groups of pathological findings, so that the technique and severity of the operation *per se* was the same as in the latter series. The mortality of the latter, therefore, cannot be ascribed to the operation itself, but is unquestionably due to the inferior condition of the patient at the time the operation was undertaken. The deaths occurred after the operation and in spite of it, but certainly not on account of it. In other words, the mortality which is so often urged against operations in the acute stage really represents the mortality of delay, with the consequent increased toxemic state. Burgess (Brit. Med. Jour., Jan. 25, 1908).

Analysis of the after-effects of operation in 640 cases of appendectomy, the time elapsed varying from five to twenty-one years. The writers found that the patients in drained cases were more likely to have a hernia in the cicatrix following operation, while the patients of undrained cases are less likely to have such a hernia. Ninety-four and six-tenths per cent. of the patients were in good health and were relieved by the operation, and 4.6 per cent. had poor health. There was definite pathological reason for the persisting poor health. In 88 patients, 13.7 per cent. of the 640 cases, the discomfort, which was of varying degrees of severity, might have been occasioned by adhesions following operation. The statement sometimes made that appendectomy is associated with distressing sequelæ is not sustained by this series of cases. Nor is the statement that appendectomy is often followed by no relief of symptoms borne out, 94 per cent. having been completely relieved. Scudder and Goodall (Boston Med. and Surg. Jour., July 6, 1911).

In 611 appendectomies during the past four and one-half years, there was a total mortality of 29 cases (4.7 per cent.). The fatal cases occurred among those operated on during the intermediary stage, late in the disease, or as a last resort. Conversely, in 80 cases of early intervention and in 306 operated on during the intervals as a pre-

ventive against recurrences, there was no mortality. Lexer (Inter. Jour. of Surg., July, 1911).

In 1700 operations for acute appendicitis operated by the writer there were 66 deaths, a mortality of 3.7 per cent. The series included all cases of acute appendicitis with and without preoperative complications directly due to the condition of the appendix or to the involvement of other viscera. Of the complications, fecal fistula occurred in 42 cases, secondary abscess in 30 and intestinal obstruction in 27 cases. An analysis of the cases of obstruction shows that fully 70 per cent. required drainage at the original operation. There is no doubt that in every case of acute appendicitis requiring drainage operation was delayed beyond the most favorable moment. J. B. Deaver (Trans. Med. Soc. State of Penna.; Jour. Amer. Med. Assoc., Nov. 23, 1918).

Cases of simple catarrhal appendicitis with adhesive peritonitis almost invariably get well. Those in which extra-peritoneal perforation occurs generally recover, unless the abscess opens into the bladder or the pleura, when recovery is doubtful. When perforative peritonitis occurs, however, the chances of recovery are greatly reduced.

In children the prognosis is, as a rule, favorable if operative procedures are resorted to early. A peculiarity in them is that the case becomes rapidly worse if left untreated. Operation during the interval is practically free from risk in patients in poor condition.

Tendency to recurrence is one of the marked features of appendicitis. The danger to life increases with each successive attack.

MEDICAL TREATMENT.—Medical treatment is indicated in only two conditions: (1) when operation is absolutely refused, and (2) while endeavoring to establish the diagnosis.

The best results in acute appendicitis can be obtained only by operating immediately after the onset of the disease, before any purgative medicine has been given and before peritonitis has occurred. Practically, if not actually, all the patients with perforative appendicitis seen by the writer have been purged, have received calomel, salts, castor oil, or some other aperient. The writer considers it practically criminal to administer a purgative in an "acute abdomen" until the cause is determined; but one drug that he knows of can be of use, namely, morphine, and this should not be given until the diagnosis is made. After the diagnosis, morphine is permissible while preparing for operation or in the enforced absence of operation. The more common causes of acute abdomen, exclusive of the traumatic conditions, such as ruptured liver, spleen, kidney, bladder, etc., are acute appendicitis, acute cholecystitis, perforated duodenal and gastric ulcer, acute intestinal obstruction, acute pancreatitis, mesenteric thrombosis, twisted pedicle of an ovarian tumor, or pedunculated fibroid, a ruptured extra-uterine sac, and acute pyosalpinx. Can any of these conditions be improved by a purge? Are they not all made worse by a purge? Again, are not all these conditions amenable to surgery alone? J. B. Deaver (N. Y. Med. Jour., Feb. 10, 1912).

The writer noticed cases with perforative lesions in the appendix were invariably those in which castor oil had been taken recently. Nearly all the patients stated that soon after taking the oil pains had set in with great intensity. Sorge (Therap. Monats. Mar., 1913).

For travelers in localities lacking experienced surgeons and hospital facilities, the essential features of medical treatment in appendicitis are **dorsal decubitus, liquid food, enemas of warm water, egg yolk, and sweet oil, warm flannels wrung out of alcohol and water and applied to the belly, covered with rubber tissue, and**

renewed when dry, and codeine tablets $\frac{1}{10}$ grain (0.006 Gm.) every 2 hours until pain is notably less, then less frequently. Transport from the bed or sitting up is forbidden so long as pain continues. **Cracked ice and good brandy** (a teaspoonful frequently) will relieve nausea or weakness. Strong broths or milk alternately or mixed together (1 or more ounces every 2 hours) should be given when prostration exists. Beverly Robinson (Med. Rec., Mar. 22, 1913).

The only death in the writer's 71 laparotomies last year was in a case of appendicitis in which a saline purgative had been given the woman behind the attending physician's back. Peritonitis followed, in spite of the prompt operation. E. R. de Aragon (Revista Med. Cubana, July, 1918).

The prevailing method is **Ochsner's**, of Chicago, who advocates a palliative treatment. In acute cases he gives: (1) **no food or cathartics by the mouth**; (2) **lavage** if nausea and vomiting occur; (3) **nutrient enemata**; (4) **water by the rectum**.

After the patient is free from pain and normal four days, fluids are gradually given by the mouth.

He operates on admission unless the case is very bad and inflammation has extended beyond the appendix. The **starvation treatment** above outlined is then continued until operation would be safe or until a circumscribed abscess forms which can be opened.

In addition to this may be added the **Murphy method of proctoclysis** in cases of appendicitis with peritonitis, with and without operation. In this procedure the fluid—warm **saline solution** [5j (4 Gm.) of **sodium chloride** and 5j (4 Gm.) of **calcium chloride** to each pint of water] at a temperature of 100° F.—is allowed to slowly drip into the rectum and be absorbed. The appa-

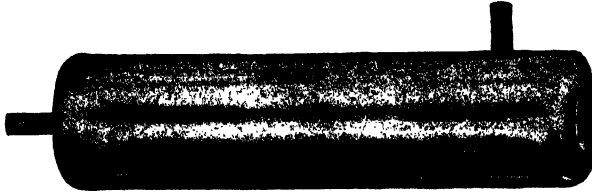


Fig. 1.—(One-third size). Represents a metal heating chamber, block-tin lined, with opening for electric heating unit and rubber-tube connections for intake and outlet of saline solution.

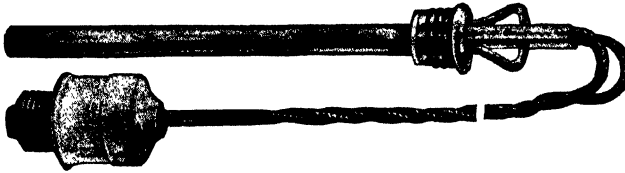


Fig. 2.—(One-third size.) Electric heating unit with socket connection and ten feet of cord. This unit can be used with either alternating or direct current 105 to 128 volts. See Fig. 8.

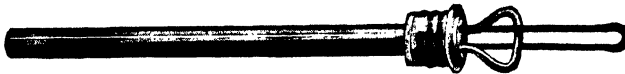


Fig. 3.—(One-third size.) Heat unit for alcohol or Bunsen burner flame with regulating piston. For use where electric current is not available. See Fig. 9.



Fig. 4.—(One-half size of largest rectal tips.) Self-retaining rectal tips on catheter showing how adjustment can be accomplished by merely drawing catheter through to desired length.



Fig. 5.—(One-half size.) Pinch cock used entirely to close flow or for drop method

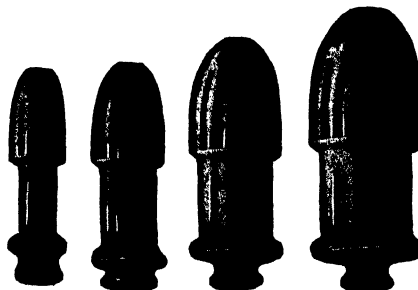


Fig. 6.—(One-third size.) Self-retaining rectal tips made in four sizes of hard rubber with opening through center to admit a soft-rubber rectal catheter, American size, No. 15. See Fig. 4.

Heating apparatus and tips for proctoclysis. (*Murphy.*)
(Journal of the American Medical Association.)

ratus should be so arranged that about 18 pints (540 c.c.) are consumed in twenty-four hours. The fluid may be kept at an even temperature by an ingenious apparatus shown in the annexed illustrations.

The tank, however, should be about 6 inches above the buttocks. This is to be continued three days, and the patient should be in the position advocated by Fowler—on the back, with the knees

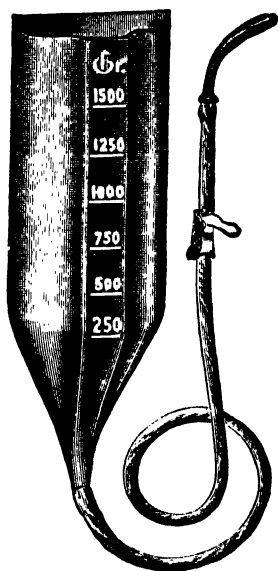


Fig. 7.—Proctoclysis apparatus consisting of fountain syringe, large rubber tube and vaginal hard-rubber or glass tip. (Murphy.) (Journal of the American Medical Association.)

raised and the head of the bed elevated about 12 to 16 inches. The patient may be allowed to rest and the fluid stopped for an hour two or three times in the twenty-four hours.

This treatment, however, is apt to lead to dangerous complications if not preceded by operation. As a postoperative measure it is of great value.

Several years ago the writer published the following conclusions after testing them carefully for a period of eight years. This form of treatment has been used by himself and many

others, in thousands of cases belonging to this class, with the result of reducing the mortality in this most fatal form of appendicitis to less than 2 per cent., by changing an extremely dangerous acute into a comparatively safe internal condition:—

1. Patients suffering from chronic recurrent appendicitis should be operated on during the interval.

2. Patients suffering from acute appendicitis should be operated on as soon as the diagnosis is made, provided they come under treatment while the infectious material is still confined to the appendix, if a competent surgeon is available.

3. Aside from insuring a low mortality, this will prevent all serious complications.

4. In all cases of acute appendicitis, without regard to the treatment contemplated, the administration of food and cathartics by mouth should be absolutely prohibited and large enemata should never be given.

5. In case of nausea or vomiting, or gaseous distention of the abdomen, **gastric lavage** should be employed.

6. In cases coming under treatment after the infection has extended beyond the tissues of the appendix, especially in the presence of incipient diffuse peritonitis, conclusions 4 and 5 should always be employed until the patient's condition makes operative interference safe.

7. In case no operation is performed neither nourishment nor cathartics should be given by mouth until the patient has been free from pain and otherwise normal for at least four days. The same practice should be followed after operation.

8. During the beginning of this treatment not even water should be given by mouth, the **thirst being quenched by rinsing the mouth with cold water** and by the use of **small enemata**. Later **small sips of very hot water** frequently repeated may be given, and still later **small sips of cold water**. There is danger in giving water too freely, and great danger in the use of large enemata.

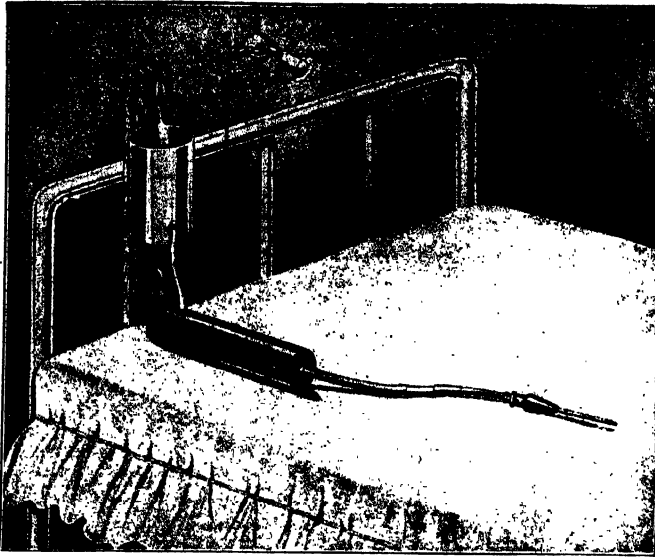


Fig. 8.—Electric heater in operation, showing it properly connected. A short glass tube connects catheter to rubber tubing.

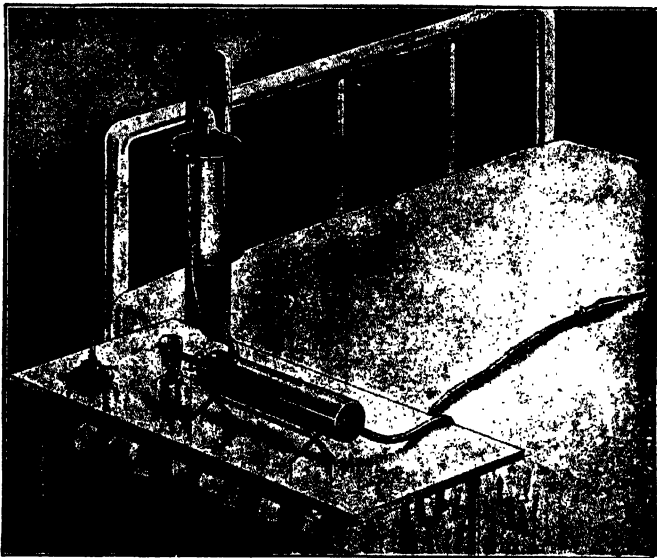


Fig. 9.—Alcohol or gas heater in operation, showing it properly connected. A short glass tube connects catheter to rubber tubing.

Proctoclysis apparatus ready for use. (*Murphy.*)
(*Journal of the American Medical Association.*)

9. All practitioners of medicine and surgery, as well as the general public, should be impressed with the importance of prohibiting the use of cathartics and food by mouth, as well as the use of large enemata, in cases of acute appendicitis.

10. It should be constantly borne in mind that even the slightest amount of liquid food of any kind given by mouth may give rise to dangerous peristalsis.

11. The most convenient form of **rectal feeding** consists in the use of 1 ounce (30 c.c.) of one of the various concentrated liquid predigested foods in the market, dissolved in 3 ounces (90 c.c.) of warm normal salt solution, introduced slowly through a soft catheter, inserted into the rectum a distance of two or three inches.

12. This form of treatment cannot supplant the operative treatment of acute appendicitis, but it can and should be used to reduce the mortality by changing the class of cases in which the mortality is very small after operation. This applies particularly to severe acute perforative or gangrenous appendicitis more than thirty-six or forty-eight hours after the beginning of the acute attack.

To conclusion 8 the writer now regularly adds the excellent method introduced by Dr. Murphy, of administering a continuous enema of **normal salt solution** with an apparatus which permits the flow of only a drop at a time, so that it will require at least one hour to introduce 1000 c.c. (1 quart).

The plan is simply this: In acute appendicitis neither food nor cathartics of any kind whatsoever should be given by mouth nor large enemata except by the drop method, and operation should be performed only when the patient has attained a condition in which the surgeon can reasonably expect a favorable result, judging from his personal observation in previous similar cases. A. J. Ochsner (Jour. Amer. Med. Assoc., Aug. 22, 1908).

The good results of the **Murphy-Fowler method** are due neither to the

elevated posture nor to proctoclysis, but to **stomach lavage and abstinence from food and purgatives** as originally proposed by Ochsner. In the treatment of desperate cases of diffuse peritonitis Ochsner advised to "splint the bowel" with opiates, abstain from giving food and purgatives, and use stomach lavage. The common error has been to regard the paralysis of the bowel as a vicious complication; on the contrary, it is nature's effort to limit and help encapsulate the infection. G. S. Brown (Surg., Gynec., and Obstet., Dec., 1909).

The Ochsner method of absolute starvation for four days is not applicable in children. The only safe course is operation, and this should be urged even during the first forty-eight hours because of the inability to predict the subsequent course of the disease, especially as in these patients the symptoms are so misleading and the margin of safety is small. During the second stage of the disease operation should be advised, but as little manipulation as possible should be observed. After the subsidence of a case the appendix should always be removed. The keynote of treatment is operative procedure at the earliest possible moment. Harold Collinson (Practitioner, July, 1911).

Even though perforation ensues, if purgatives are not given and absolute starvation is enforced, diffuse peritonitis does not as a rule supervene, a localized abscess usually developing. This fact affords the best indication for treatment: At the onset **all food** by mouth should be **withheld**, to arrest peristalsis and reduce virulence of the bacteria. **No purgative** should be administered and even the giving of fluids, which must reach the cecum to be absorbed, should be avoided. H. A. Bruce (Can. Med. Assoc. Jour., May, 1912).

I agree fully with Collinson and would go farther, and in stout adults I do not believe the Ochsner treatment is indicated, except in the pres-

ence of very strong contraindication to operation.

For the pain, the suspended ice-bag, or frequently changed cloths wet in ice water, may be applied over the cecal region. If this is done frequently enough the pain can be kept in abeyance.

Opium was at one time highly recommended, but it is now regarded by practically all clinicians as a dangerous remedy. It masks the symptoms, and thereby tends to compromise the chances of operative procedures through delay; it locks the intestines and thereby prevents the expulsion of infectious discharges.

Opium is sometimes used in light cases in which we feel certain that no aggravation of the condition present can occur. But this no one can foretell with certainty, and it seems best to protect the patients against increased chances of death by employing only local anodyne measures that will not mask the advance of complications.

In children with early diagnosis and operation the prognosis is favorable, but it rapidly becomes worse after twenty-four hours. In chronic appendicitis an acute attack with perforation is always to be feared. In intra-appendiceal appendicitis complete removal of the appendix and the diseased surroundings is advised. Non-operative treatment is indicated in localized abscess with diffuse peritonitis. Opium and purgatives are absolutely contraindicated. Operation is even more suitable to children than to adults, and postoperative treatment is very important. The Fowler position must not be kept up for more than thirty-six hours in drainage cases lest intestinal obstruction be set up. H. C. Deaver (Jour. Amer. Med. Assoc., Dec. 24, 1910).

The cases of acute appendicitis which should not be operated on immediately are those with diffuse peri-

tonitis, usually but not necessarily of more than 48 hours' duration. These, if rigidly treated by rest, proctoclysis, absolutely nothing by mouth, with lavage if necessary, the sitting position, and the ice-bag or ice-coil, with few exceptions end in recovery from the spreading peritonitis. The localization of the mischief thus allows of operation, which should then be done immediately. Deaver (N. Y. Med. Jour., Feb. 10, 1912).

The colon bacillus and streptococcus vaccines are recommended by the writer in acute appendicitis in conjunction with operative treatment, 2 g. 50,000,000 dead colon bacilli on the first day, 100,000,000 on the second, 200,000,000 on the third, and 400,000,000 on the fourth. Many of his cases with tumor and fever either passed rapidly into the "cold" stage, where simple drainage, or drainage with appendectomy, became possible, or, when suppuration was slight, convalesced without drainage. W. W. Crawford (So. Med. Jour., June, 1912).

If operated upon early, liberal doses of vaccine are helpful unless the patient is already overwhelmed with toxins. The writer employed anti-colon-bacillus serum and vaccine in 22 cases, which recovered without operative measures. Most of the cases were acute. The best dosage was 20 c.c. (5 drams) of anticolon-bacillus serum, 10 c.c. (2½ drams) being injected subcutaneously first in the right and then the left hypochondriac region. A few days later 100 million colon-bacillus vaccine is injected in the deltoid region, to prevent recurrence. As other organisms may be causative, the 'fixation of complement test' should be tried, using the patient's serum and the most probable organism (*B. coli*, pneumococcus, streptococcus). A corresponding serum or vaccine is then used. A striking relief of pain and a feeling of well-being followed the employment of serum injections. A. C. Guthrie (Brit. Med. Jour., Jan. 9, 1915).

The writer found chronic appendicitis unmistakable in over 33 per cent. of 145 cases of gastro-enterostomy for ulcer. In private practice, this percentage is even higher. The frequency of such associated lesions explains the failure to cure of operations on one of the lesions, leaving the others still in a position to cause disturbance. They indicate the necessity for careful exploration of the entire digestive tract. In 33 per cent. of 36 laparotomies for ulcers and pyloric stenosis, the appendix was found diseased, as also in 45 per cent. of forty operative duodenal ulcer cases. Moreover, 80 per cent. of the gastric ulcer cases presented evidences of pulmonary tuberculosis at the time, florid, torpid or healed. In nearly or quite all of them, pressure on the pneumogastric nerve in the neck on one or both sides was painful. The writer calls this the "sign of the pneumogastric," and explains it as a neuritis of this nerve, of pulmonary origin, and possibly reflected along the entire gastro-intestinal distribution of these nerves. This affords a predisposition to trophic disturbance, liable to elicit ulceration and certain other chronic inflammatory processes in the alimentary canal. Dubard (Lyon Chir., May-June, 1918).

The general practitioner should refer his cases earlier to the surgeon. This would reduce the number of drainage cases, which later are nearly always followed by an incisional hernia. Some types of acute appendicitis ought to be operated on at once. Others are benefited by a rest of a few hours by instituting the Fowler-Murphy treatment. Children should be operated on at once on account of the peculiarity of the appendix of undergoing rapid inflammatory changes. Behrend (Therap. Gaz., March 15, 1921).

SURGICAL TREATMENT.—Operation is indicated when the diagnosis is made, unless the appendicitis be the result of some other acute disease, typhoid fever, for instance, or when a

sufficiently competent surgeon cannot be obtained. Under the latter conditions the patient should be kept in bed and the bowels moved by **enemata**, and the pain kept down by **ice compresses** or the suspended **ice-bag**, as previously stated. Persistent vomiting should be met by **washing out the stomach and rectal feeding**. Otherwise, a **liquid diet** by the mouth is permissible.

Laxatives are distinctly contraindicated in *appendicitis in children*, as in adults. If nausea and vomiting continue, **gastric lavage** is invaluable. A small enema to relieve the colon may be given. In reality, there is no medical treatment for appendicitis in a child unless operation is refused. **Morphine** can then be used to relieve pain. **Saline enteroclysis**, if taken kindly, is apparently valuable. No water or food should be given except in rare instances. Every child with acute appendicitis should be operated if seen early. Aynesworth (Amer. Jour. of Obstet., Nov., 1915).

The writer makes the following recommendations: (1) examine the patient thoroughly and not through the clothes; (2) give no aperient; (3) $\frac{1}{2}$ to $\frac{1}{16}$ grain (0.005 to 0.004 Gm.) of **morphine** will not mask the symptoms and may be safely given when the pain is severe; (4) the diagnosis having been made, operate. In the presence of peritonitis and in the absence of operation, **set the patient up in bed**, give **nothing by mouth**, place an **ice-bag** over the tender area, and institute **enteroclysis**. Operate in the cases of localized peritonitis where the lesion can be localized and there is peristalsis in the surrounding region of the abdomen. In diffused peritonitis defer operation until the peritonitis becomes a localized or localizing one. Deaver (N. Y. Med. Jour., Feb. 5, 1916).

The writer operated 324 consecutive cases of appendicitis at the Naval Hospital at Norfolk, Va., without a death. Of these, 183 were acute and 141 chronic, interval operation being

included in the latter. Immediate operation was done in all cases with acute symptoms. R. B. Williams (Surg., Gynec. and Obstet., Feb., 1916).

A warning is published by the writers against the impression that appendix cases should not be operated upon after the third day unless or until a localized abscess has evidently formed. An inflamed appendix should be removed immediately, no matter what day of the disease. Fever is by no means a constant symptom of a gangrenous appendix or localized peritonitis. Inversion of the appendiceal stump is opposed by the author, the stump being a potential source of infection, and the general peritoneum being better able to deal with it than the tiny sac of peritoneum with which it comes in contact after application of a purse-string suture. Inversion of the stump without primary ligation is inadvisable also, because of the danger of hemorrhage. In all pus cases immediate use of a stock mixed infection vaccine is urged. The **Fowler position** and **Murphy drip** are also used, and, if post-operative ileus is feared, injections of **eserine**. Secord and Coates (Can. Med. Assoc. Jour., vi, 421, 1916).

The writer does not recommend the interruption of pregnancy. During the operation the uterus should be handled as little as possible and later opiates should be administered. The operation may be performed under local or general anesthesia. The operation of choice is **appendectomy**. A. P. Heineck (Med. Fortnightly, May 15, 1917).

In 1700 operations for acute appendicitis collected from his recent records at the Lankenau Hospital, 66 deaths gave a mortality of 3.7 per cent. The series included all cases of acute appendicitis with and without preoperative complications directly due to the condition of the appendix or to the involvement of other viscera. Of the complications fecal fistula occurred in 42 patients,

secondary abscess in 30, and intestinal obstruction in 27. An analysis of the cases of obstruction shows that fully 70 per cent. required drainage at the original operation. There is no doubt that every case of acute appendicitis requiring drainage could safely be taken as an indication that operation was delayed beyond the most favorable moment. In the prevention of surgical complications nothing is more important than to forestall the formation of pus within the peritoneal cavity. In adhesions and consequent obstruction a large number of these cases would not have developed if the original appendicular disease had been treated early and no drainage had been required. In practically every death from appendicitis some one is to blame. The question is who is at fault. Is it the parent or friend who refuses consent, or is it the ill advised administration of an aperient or purge? It is undoubtedly the latter. J. B. Deaver (Trans. Penna. State Med. Soc.; N. Y. Med. Jour., Mar. 8, 1919).

When the operation can be resorted to, the following are its various steps:—

The *incision* that is generally preferred when there is no infection beyond the appendix proper is that recommended by **McBurney** (see *b*, colored plate). It crosses an imaginary line (*a*) drawn from the anterior superior spine of the ilium (*D*) to the umbilicus (*A*) at the juncture of its middle and lower thirds, and thus overlying the diseased structures. The integument and aponeurotic structures are alone to be incised, the muscular fibers being separated by means of the scalpel handle in a line parallel to their course. As a result, muscular action will rather tend to approximate than to draw apart the edges of the wound and thus prevent postoperative hernia: a condition frequently met with, especially when the median incision was

generally used. The latter is still resorted to by some surgeons, and is especially useful when diffuse abscess is present.

McBurney's gridiron incision is ideal for a large majority of the interval operations according to Hafrington. If more room is needed the incision may be enlarged, the so-called extended McBurney incision. In nearly every case of appendicitis, it is best to enter the free abdominal cavity beyond the appendix and the inflammatory mass in order to examine for secondary abscesses and to determine the condition of the rest of the abdomen. If the appendix mass extends beyond the semilunar line it is better to open the abdomen by a vertical incision through the rectus sheath and separate the rectus muscle or to retract it. If it extends to the middle line or beyond, the opening should be in the middle line.

While the **McBurney incision** is satisfactory for a simple appendectomy, it is not suitable for the exploration of the upper abdomen so often indicated, nor does it lend itself to enlargement. Its routine use leads to otherwise avoidable technical difficulties, and conditions may be overlooked which would be observable through the right rectus incision. Brickner (*Amer. Jour. of Surg.*, Jan., 1915).

Wyeth gives preference to the **Deaver incision**, because it offers free access to the cecum and appendix, and when, as is not infrequent, it becomes necessary to have more room for safe and thorough work it can be extended indefinitely upward or downward, giving complete command of the peritoneal cavity with the minimum of risk of being followed by ventral hernia.

A **transverse incision** is advocated by the writer in appendicitis. It is made directly transverse with its

center at or near McBurney's point. In ordinary cases it should be 2 or 2½ inches in length. It passes through the outer part of the sheath of the rectus, severing the tendinous border and the aponeuroses of the muscles transversely. Then the handle of the scalpel may be inserted below and the finger above and the wound spread wide open. Not a muscle fiber is cut, the fibers of the internal oblique and transversalis being separated transversely. The aponeurosis of the external oblique is broader than that of the other muscles, thus permitting the incision through this to be carried further to the outer side. A. E. Rockey (*Jour. Amer. Med. Assoc.*, Sept. 11, 1915).

The frequency of postoperative hernia has caused surgeons to greatly reduce the length of incisions, and Morris has shown that an opening through the muscular tissues 1½ inches in length was sufficient in the majority of instances. McBurney has found that even in his method the opening in the deeper layers of the abdominal wall need not be more than 2 inches in length. It has been proposed to shorten this incision to ½ inch. No rule can be laid down to apply to all cases. An inch incision will suffice in some cases and 3 inches will be needed in others. It makes little difference, since as with a proper closure of the wound a hernia almost never occurs at the present time.

In tracing the late results of operation for acute appendicitis in 117 cases, the writer found that hernia occurred in 20 per cent. of cases which had been drained. Among those not drained, but 1 developed hernia. Nine patients suffered from adhesions, 6 drained and 3 not drained; 14 had indigestion, 8 drained; 17 had pain of obscure cause. Constipation was rather common. Post-operative comfort depended on

prompt operation, avoidance of cathartics before operation, and minimum of drainage. G. P. Muller (N. Y. Med. Jour., Oct. 30, 1915).

McBurney recommended his method only for non-suppurative cases or those in which drainage was not required, but many surgeons employ it with advantage in almost all cases of appendicitis, including those in which an abscess is present and where drainage is required.

Some operators have found that when the appendix is in the normal position and is not difficult to bring out McBurney's method is almost ideal; but when difficulties arise and the incision has to be enlarged, the necessarily constant and hard retraction of the muscles is likely to injure the tissue and sometimes to cause suppuration. If it is necessary to enlarge the wound, there results a ragged and complicated wound, not well adapted to drainage if pus is found. The position of McBurney's incision is also thought by some to render proper drainage difficult to obtain. Other incisions are, therefore, resorted to.

That preferred at the present time, under these conditions, is the incision designated by a dotted line in the annexed colored plate (*d*) along the outer border of the rectus muscle, beginning slightly below the level of the umbilicus and extending downward, in a straight line, 2 or more inches, according to the operative area desired.

This same incision, amplified by another, has been recommended by Jalaguier, which is especially applicable to cases occurring in slim children. It is thought to prevent postoperative hernia better than any other. The skin and the aponeurosis of the external oblique are incised at the outer border of the rectus (*d*), and the aponeurosis on the inner side of this incision is then dis-

sected for some distance from the anterior sheath of the muscle, and drawn toward the median line, exposing the sheath. An incision (*c*) parallel to the first is then made in the latter sheath about $\frac{1}{2}$ inch to the inside of the border of the rectus, exposing the muscle. When the operation is finished, the deeper incision is closed and the rectus, permitted to slip in place, acts as protecting covering. Deaver and many other surgeons now use the incision along the rectus alone; also in adults for all cases of appendectomy.

Modified incisions have also been proposed by other surgeons, among which those of Elliott, Vischer, Willy Meyer, Fowler, and Weir may be mentioned.

The abdominal walls having been penetrated, the margins of the wound are then retracted by an assistant, unless the abscess has already reached the surface. The peritoneum is then divided freely, but with great care. Any pus encountered is carefully sponged out.

The handling of the intestines, and even their exposure to the air, is one of the most potent causes of shock after abdominal operations. The use of gauze packings, even of the temporary variety, causes subsequent shock, and, by injuring the delicate serosa, determines the formation of postoperative adhesions. So well known is this method of producing shock that the handling of the intestines is a favorite method for producing this condition in animals for purposes of study. Little handling causes less shock; much handling causes profound shock. To lessen this element of danger in **appendectomy**, the following method will be found valuable according to Lilienthal:

Through a small incision made in the locality preferred by the operator,

a gloved finger is inserted, locating the cecum; a portion of this viscus is withdrawn with dressing forceps, and landmarks followed in the usual way to locate the base of the appendix. During this procedure there will be a little unavoidable handling of intestine outside of the abdomen. Having exposed the base of the appendix, a ligature is passed through the mesentery, to be used subsequently for ligating the organ; the ends of this ligature are left long, and are tied together or held with a clamp. The exposed part of the appendix and all other intestines are now returned to the abdominal cavity. When traction upon the ligature is made the base of the appendix and *nothing more* is brought into the wound. In the majority of cases it will be found extremely simple to deliver the entire appendix even though a considerable number of adhesions should be encountered. The ligation of the mesenterium, the ablation of the appendix, and the treatment of the stump are carried out in the usual manner. During the procedure of freeing and removing the appendix, this organ and nothing else is in the field. It is useful in most interval cases and in the early stage of the acute forms.

Matted coils are *gently* separated, and intestinal prolapse and contact with diseased surfaces are prevented by carefully packing the cavity around the cecum with pads of sterile gauze, the ends remaining outside or being held by clamps. This should be done in such a manner that no infected tissue or fluid be in any way brought in contact with the healthy peritoneum. The walls of the pus-cavity are then disinfected with a **bichloride solution** of 1:5000.

The cecum being now isolated, it is important also to remove the cause of

the abscess or its contents without causing septic material to invade the general peritoneal cavity.

If the appendix is not readily found, the anterior longitudinal band of the cecum is taken as a guide and followed until the appendix is encountered—usually behind.

In the Rangoon Hospital it was observed that when a small incision had been practised and the appendix was difficult to find, salt solution poured into the abdomen made the appendix float up into the wound. Clopton (*Interstate Med. Jour.*, Aug., 1910).

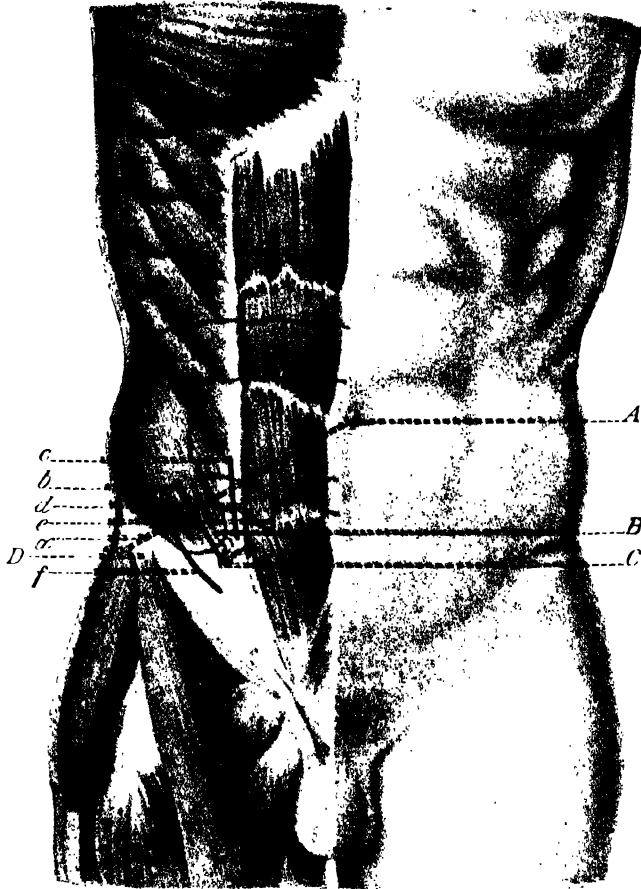
In the annexed colored plate only the tip of the appendix shows; but the greater part of the organ lies behind the cecum, its orifice in the latter being situated immediately under the spot where the McBurney incision (*b*) crosses the index line (*e*).

Adhesions are often encountered; care should be taken, when separating them, to protect the general peritoneal cavity with sterile gauze, as they are often septic.

The possibility of an anomalous conformation or position of the appendix should be borne in mind.

When located and brought out, the appendix should be clamped close to the cecum, cut off on the distal side of the clamp, closing the opening by means of a double row of Lembert (silk) sutures. The appendix is sometimes found detached and necrotic.

If there is a circumscribed abscess, it is poor surgery to insist, in every case and at every period, upon finding and taking away the appendix in the face of all obstacles. In many cases of circumscribed abscess, and especially in those in which the appendix is bound down by adhesions in the depth of the wound, the surgeon should be content with evacuation, irrigation, drainage, and



Incisions for Appendicitis.

A umbilicus ; *B*, cecum and termination of the ileum ; *C*, vermiform appendix ; *D*, anterior superior spine of the ilium ; *b*, McBurney's incision ; *d*, the Jalaguier-Deaver incision.

packing with plain gauze. Persistent search for the appendix and attempts at its removal in these cases are attended with such danger of opening the peritoneal cavity that they are not to be recommended.

A series of 110 cases of appendicitis, operated without mortality. When free pus is present with extensive peritonitis, the writer sponges it out whenever seen. One or 2 long retractors are then passed into the pelvis and the patient tilted to the right side, allowing removal of pus without passing sponges into the pelvis. No attempt is made to investigate. One or more drains are placed in position and the wound partially closed. Soft rubber drains or iodoform gauze covered with green gutta percha are employed. No rubber tubing or gauze is left in contact with the intestines. In cases with marked vomiting or with free pus and extensive peritonitis, the stomach is washed in the operating room as soon as the binder is put on. The **Murphy drip** is used in a large proportion of cases. One dose of $\frac{1}{4}$ grain (0.016 Gm.) of **morphine** is given if pain is severe, with a second dose of $\frac{1}{2}$ grain (0.008 Gm.) if necessary to insure a comfortable night. Nothing is allowed by mouth, even water, for 24 hours in the severe cases. After 36 or 48 hours, a low enema is given; if satisfactory, no further attention is paid to the bowels for 24 hours, when 1 dose of 3 grains (0.2 Gm.) of **calomel** and 10 grains (0.6 Gm.) of **sodium bicarbonate** is given, followed in half an hour by a **seidlitz powder**. W. B. Brinsmade (*Annals of Surg.*, Nov., 1914).

Patients with gangrenous, purulent, or perforative appendicitis refer to chills or chilliness, experienced at the very beginning or in the first few hours of the attack. In cases with history of such a chill he urged operation as more imperative, and anticipates drainage as being necessary. Where an ice-bag or cold had been applied before operation there was

noticed a lack of effort on the part of nature to wall off the appendix, which was frequently much congested, perforated or gangrenous. Where a **hot water bag** or moist heat had been employed a greater attempt toward walling off was manifest. Acute pain stopping in 24 to 48 hours, with marked rigidity, suggests gangrene or acute stasis and is often followed in 12 to 24 hours by sudden pain indicating perforation. The temperature and pulse rate are untrustworthy as indicators of safety. F. C. Warnshuis (*Lancet-Clinic*, Sept. 9, 1916).

The **stump** is either simply disinfected or the mucous membrane of cut surface cauterized with **carbolic acid** or **cautery**. The latter procedure is generally unnecessary, however. If the tissues about the base of the appendix are nearly normal, it is better to invert the stump and close it with two or three Lembert sutures. If not, a simple ligature on the proximal side of the clamp is usually sufficient.

In response to circular letters sent to a number of surgeons, 64 replies were received, representing 80,251 appendectomies, with an average mortality of $7\frac{1}{2}$ in acute, and $1\frac{3}{4}$ per cent. in chronic, cases. Eighty per cent. of the total number of operations reported have been done by the four purse-string methods. The acute and chronic cases were about equal in number. (Of the 60 hemorrhages mentioned, all but 1 resulted in the purse-string methods. Investigation of this subject shows that many operators have abandoned the purse-string methods; that others are doing so; that simple ligature for the firm, and extirpation for the soft, appendix are safer. B. M. Ricketts (*Surg., Gynec., and Obstet.*, Jan., 1908).

The writer is convinced that it is not yet safe to let the order go out that the simple ligation of the appendix, without any further protection of the stump, is ample. He feels that we should give an additional protection to

that stump other than mere ligation in the acute infected cases. These are the cases in which we are most likely to have leakage when we simply tie the stump and cut it off. In the intermediate cases, in which there is no infiltration, no reaction to inflammation at the time, the writer treats it by clamping, by tying a ligature in the crease, and then by taking an overstitch so that there is no raw or abraded surface at that point to become adherent, and it will not become adherent. In the active cases he ligates and then puts in a drain. J. B. Murphy (*Jour. Amer. Med. Assoc.*, Aug. 22, 1908).

The writer objects to burying the stump for the following reasons: 1. It is more complicated than the simple ligation of the appendix, an intestinal suture being used in addition to the ligature. 2. The purse-string suture cuts off some of the blood-supply which would otherwise go up to the ligated stump and assist in healing. This also diminished the resistance of the tissues. 3. It places a piece of necrotic tissue, the stump, in a closed cavity, and shuts it off from the omentum which would not only help to absorb the stump, but would also be a safeguard against infection. 4. By burying the stump and cutting off some blood-supply, a greater hyperemia is caused than when the stump is simply ligated; consequently, the adhesions that occur are more likely to be permanent, for when the stump adheres it is absorbed. 5. It offers an excellent place for abscess formation, having most of the requisites, *i.e.*, a closed cavity, diminished blood supply, a piece of necrotic tissue, and being almost totally surrounded by fecal contents of the cecum. 6. It tends to leave a permanent lump in the bowel wall, which will be a constant source of irritation and a possible starting point for cancer. J. Shelton Horsley (*Trans. So. Med. Assoc.; N. Y. Med. Jour.*, Apr. 21, 1917).

Drainage is to be maintained until healing is shown to be taking place from

the bottom of the wound. Gauze is to be used not only for the purpose, but quite as much to stimulate the adhesions between coils of intestine which surround it and to shut off the general peritoneal cavity from the infected portion. A simple cigarette drain answers all purposes.

The introduction of the gradual method of **enteroclysis** by Murphy has added wonderfully to the successful treatment of this condition. It is remarkable how drainage will be increased under the circumstances. The fluid seems to percolate through the intestines and find its way toward the dressings, thereby largely carrying out the infectious fluids. Before the use of the gradual enteroclysis, dressings would remain quite dry, showing very little secretion. This would indicate very bad prognosis. Ernest Laplace (*Penna. Med. Jour.*, March, 1908).

It is important to withdraw the gauze plugs by rotary movement rather than by direct traction; it causes less pain. The patient should be revived from the shock of the operation as early as possible by an **enema of hot coffee or whisky**.

Remote Abscesses.—While most abscesses are found in the appendicular region, others may occupy areas quite remote from the latter, including, we have seen, the lungs.

The most common method of extension from the original focus of supuration in the appendiceal region to the thorax is either intraperitoneally or extraperitoneally behind the kidney, first to the subphrenic space, thence through the diaphragm to the adjacent pleura, and finally to the contiguous portion of the lung with probable communication with the bronchus. In this way the abscess is frequently evacuated through the mouth. More rare methods by which these sequelæ may occur are either by localization of a general systemic infection or by the appearance in

the pleura or lung of one or more abscesses which arise in the course of a secondary pyemia. These sequelæ of appendicitis occur in not less than 2 or 3 per cent. of all suppurative cases. Gage (Boston Med. and Surg. Jour., April 11, 1907).

To properly locate a remote abscess is of great importance. When its evacuation becomes necessary the selection of the best point for incision is in order. This subject is graphically portrayed in the annexed colored plate prepared from sketches and an interesting paper by Dr. M. L. Harris.

Description of Colored Plate on the Location of Appendicular Abscesses.—A circle of an inch and a half in diameter—the size of a silver dollar—drawn about the center of the posterior surface of the cecum will touch the base or point of origin of the appendix in about 96 per cent. of all cases. It will thus be seen how constant is the location of the base of the appendix. The average length of the adult appendix is 9 cm., or $3\frac{1}{2}$ inches. A circle, then, of 4-inch radius drawn about the same center as the smaller circle will give a very large area in the abdominal cavity, anywhere within which the apex of the normal appendix may be found located. (See illustration.)

The space within the large circle (see illustration) may be subdivided into five separate areas (marked 1, 2, 3, 4, and 5), each having distinct and well-defined boundaries. The appendix may be found in any one of these areas, and, when an abscess forms about the inflamed organ, it is the particular area in which the appendix is located which gives the abscess or exudate its characteristic location and outline, which limits its extension in one direction and favors it in another, and which should guide us in the selection of the best point for incision.

Area 1: Inframesenteric.—The appendix is met with in this area in about 60 per cent. of the cases, either superficially situated, approaching anteriorly, or lying deeply on the posterior wall; it may extend directly inward, hugging the under surface of the mesentery at the ileum, or inward and downward, reaching often into the true pelvis. The mesentery above prevents the extension of

abscesses in an upward direction, but gives them a tendency to extend forward and to the left.

The pelvic abscesses are limited in the male anteriorly by the bladder, posteriorly by the rectum and pelvic wall, and above by the sigmoid and loops of small intestine. In the female they fill Douglas's *cul-de-sac* or occupy the ovarian region on one or both sides, where they are often with great difficulty differentiated from pelvic abscesses of tubal or ovarian origin. The danger of infecting the general cavity on opening these abscesses from above is very great, and the advisability of draining through the vagina in the female, as in other septic pelvic troubles, comes into serious consideration.

The interintestinal abscesses (see also illustrations) are usually situated near the median line, and are consequently best opened at this point. Adhesions may limit them, or there may be no adhesions and the free peritoneal cavity must be traversed to reach the abscess, after packing with iodoform gauze to prevent diffusion of pus. It is often impossible to prevent pus escaping into the general cavity, with a resulting fatal acute septic peritonitis. It is in those cases that the advisability of doing a *deux temps* operation should be considered. Should the appendix be found floating free in the abscess cavity it may be removed, but if it be firmly imbedded in the exudate forming part of the abscess wall it should, under no circumstances, be torn out and removed, if by so doing we endanger breaking into the general cavity, thus leading to general sepsis.

The exudate may also come to the surface, forming adhesions to the anterior abdominal wall, just internal to the cecum. (See illustration.) The abscess is limited externally by the cecum and internally by the loop of ileum which almost always covers over the end of the cecum and the omentum. It is usually best opened by a vertical incision over the inner border of the cecum. Care should be taken not to separate the loop of intestine internally, particularly at its lower angle, as pus then escapes at once into the pelvis.

The appendix can nearly always be removed, as it usually lies posteriorly or anteriorly, and it can be done without disturbing the internal wall of exudate which protects the general cavity.

Area 2: Retrocecal.—Abscess is met in this area (see also illustration) in about 23 per cent. of the cases. The appendix lies in the little pouch posterior to the cecum, more or less curved or folded upon itself or extending downward and outward to a more or less marked degree.

It is best opened by an oblique incision parallel to the outer half of Poupart's ligament, coming down upon the outer border of the cecum, which should be raised up and turned inward. The appendix can nearly always be removed, unless it should be too firmly imbedded in the exudate forming the inner wall.

Area 3: Supramesenteric.—Abscesses here (see also illustration) have a tendency to spread toward the liver and duodenum. The appendix lies above the mesentery of the ilium and internal to the inner layer of the mesocolon.

These abscesses are best reached by an incision along the external border of the right rectus muscle, great care being taken not to break down the adhesions between the loop of small intestine to the inner side. (See incision *c* in first colored plate.)

Area 4: External.—This is the space between the outer border of the colon, with its outer layer of mesocolon, and the external abdominal wall. The appendix may extend upward and outward into this space, its tip sometimes reaching nearly to the under surface of the liver. Abscesses spread to the liver and have repeatedly ruptured into the pleura and even into the bronchi. (See illustration.)

They may be reached by an oblique incision extending from above the crest of the ilium downward and inward, parallel to the outer third of Poupart's ligament, or, if the abscess is high up, by a longitudinal incision over its most prominent part, care being taken to not injure the iliohypogastric nerve. The appendix can nearly always be removed, as there is no danger, in separating the adhesions about it, of opening the general cavity.

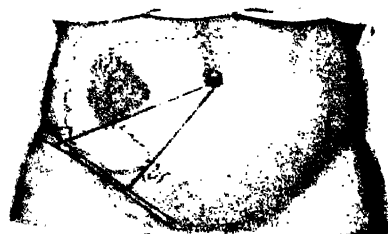
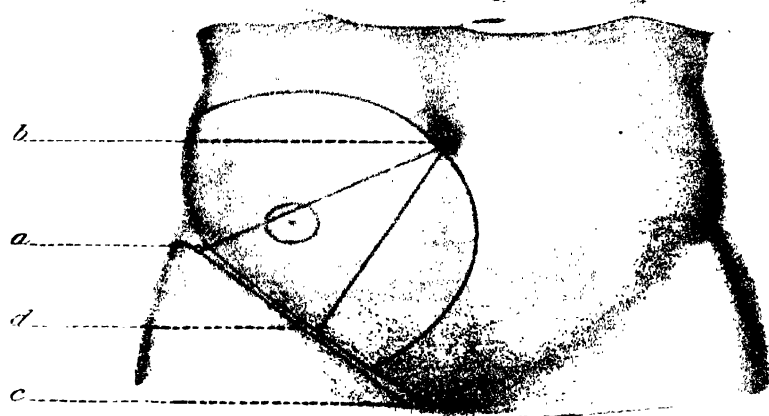
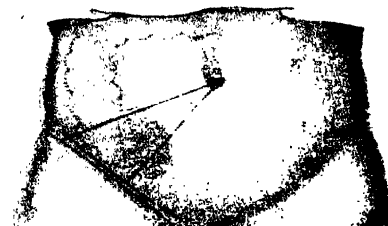
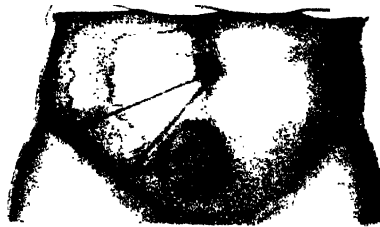
Area 5: Retrocolonic, or Extraperitoneal.—In the cellular space posterior to the colon between the two layers of the mesocolon. (See illustration.) Abscesses here are entirely extraperitoneal. The colon is pushed forward.

Subphrenic Abscess.—This complication of appendicitis was thought at one time to be quite rare, but recent developments have shown that this was due to the fact that they were seldom diagnosed. As stated by Christian and Lehr, they may occur in one of four ways: As a localized abscess, a part of general purulent peritonitis; by extension of the diseased process from the appendix to the subphrenic region by an intraperitoneal route; by extension of the diseased process by an extraperitoneal route, either by way of the lymphatics or by infiltration through the retroperitoneal tissue; by way of the blood-current as part of a general embolic septic process, or as a sequence of liver abscesses which are of the portal vein.

Several modes of onset are characteristic according to Elsberg who bases his study on 179 cases collected by Maydl:

(a) A few days after the acute symptoms of appendicitis have been relieved and the temperature has fallen to the normal, the patients begin to complain of pain in the lower part of the right chest, the temperature begins to rise, the area of liver dullness is found to be somewhat enlarged, there are friction sounds over the hepatic region, and tenderness in one or two intercostal spaces. There may be slight or well-marked jaundice. Within a few days the pain over the liver becomes less, while the signs of fluid become evident.

(b) Before the acute symptoms of appendicitis have entirely subsided, although the local symptoms are much improved, the daily temperatures begin to take on a remittent type, and the patients begin to lose flesh and strength rapidly. These patients look very ill from the beginning. They do not com-



Location of Appendicular Abscesses. (*M. L. Harris.*)

a, anterior superior spine of the ilium; *b*, umbilicus; *c*, symphysis; *d*, Poupart's ligament.

plain of much pain, although they may have tenderness in the lumbar region; the most marked symptom is the rapid loss of flesh and strength. No further physical signs may be discoverable until the bulging of the abscess in the lumbar region is found.

(c) After having recovered from the attack of appendicitis in a satisfactory manner, some of the patients never regain their former health. Without any change in the temperature, respiration, or pulse, the patients complain of continual slight pain in the right chest. The pain persists for weeks or months; physical examination and aspiration of the right chest result negatively. The patients never look very ill. After a varying length of time, the presence of fluid under the diaphragm, and perhaps also in the pleural cavity, is discovered by means of physical examination and the aspirating needle.

There are five methods of draining a subphrenic abscess: (a) by an incision in the epigastrium; (b) by an incision along the costal arch; (c) by an incision in the lumbar region; (d) by the transpleural route; (e) by pushing the pleural reflection upward and opening the abscess cavity through an incision in the diaphragm without opening the pleural cavity. The first three methods are indicated when there is bulging in the epigastrium along the costal arch or in the lumbar region. A simple incision will suffice to evacuate the abscess. If, however, suppuration continues and septic symptoms reappear, they indicate either an accompanying empyema or insufficient drainage, or, finally, a persistence of the original focus. Eisendrath (Jour. Amer. Med. Assoc., March 7, 1908).

Subphrenic abscess following appendicitis is more common than formerly was supposed, and it occurs in from 0.5 per cent. to 1 per cent. of all cases of acute appendicitis. Various authors have agreed that infection may occur

as a part of the general peritonitis; by direct extension up the lower peritoneal fossæ; through the medium of the portal vein, and by lymphatic extension (a) up the right peritoneal cellular tissue or (b) up the lymphatics around the deep epigastric artery to the falciform ligament. The writer believes that the second of these methods of approach is by far the most frequent. G. C. Ross (Jour. Amer. Med. Assoc., Aug. 12, 1911).

Diffuse Abscess.—If an abscess has opened into the peritoneal cavity or the appendix has ruptured into the free peritoneal cavity, causing diffused septic peritonitis, a good-sized incision is made parallel to the border of Poupart's ligament or the ordinary McBurney incision may be made, the peritoneal cavity is opened, and the contained fluids are gently withdrawn. The appendix is removed; further collections of fluid are looked for and withdrawn with a sponge on a handle. The cavity is washed out with a saline solution, and drainage is provided for by a glass tube, or rubber tubes threaded with a capillary gauze drain. The wound is left open or closed at the ends by a few sutures. **Nutrition by rectum** is kept up for a day or two, and the deep packing is not disturbed for four days.

CHRONIC (RELAPSING, OR RECURRENT) APPENDICITIS.

SYMPTOMS.—The symptoms of an exacerbation of appendicitis—for a relapse is practically such—are the same as in the acute form, except that they are apt to be more severe and early perforation is liable to occur. The simple catarrhal form may be suspected when the recurrences (hence, *recurrent appendicitis*) happen more than four or five times, and last not more than a week, though no tumor is felt. Discomfort in the region of the appendix between the

attacks is complained of, and the appendiceal area is somewhat sensitive to pressure, and sometimes the seat of actual pain with slight fever. The attacks may be slight at first and continue to be so, but a severe and even fatal attack may occur at any time. Hence, the advisability of resorting to appendectomy during an interval. Fatigue, muscular strain, dietetic errors, etc., may bring on an attack.

An attack is usually ushered in by severe abdominal pain, sometimes beginning in the epigastrium or mid-abdomen, often with nausea and vomiting. The pain then centers itself, if it has not done so from the start, in the appendiceal region. Flatulence and a feeling of distention and diarrhea are also present in most cases.

Appendiceal dyspepsia has been characterized by symptoms strikingly analogous to the earliest symptoms of acute appendicitis, namely, attacks of epigastric or midabdominal pain or distress only rarely accompanied by subjective symptoms referable to the region of the appendix. During these attacks the pain or distress is nearly always increased by food intake. Pain confined chiefly to the right lower quadrant and not associated with attacks of epigastric pain and nausea is seldom due to the appendix. E. M. Stanton (*Annals of Surg.*, June, 1911).

Five cases of chronic appendicitis the early history of which had always been indefinite whether the symptoms were referable to the stomach, duodenum, gall-bladder, or the large bowel. A period varying from one year to several years had elapsed before any evidence strongly suggesting appendicular disturbance manifested itself. Finally, close analysis of the symptoms and repeated examinations of the abdomen warranted each time the diagnosis of chronic appendicitis. It is essential to investigate these cases thoroughly and to exclude all other pathological conditions before resorting

to surgery. Jacobson (*N. Y. Med. Jour.*, Aug. 12, 1911).

In cases of chronic appendicitis with digestive symptoms, induction of referred pain or distress in the epigastrium, left hypochondrium, umbilical, left inguinal, or precordial region by a continuous firm pressure over McBurney's point is a valuable test in deciding when and when not to recommend operation. Aaron (*Jour. Amer. Med. Assoc.*, Feb. 1, 1913).

The gynecologist finds it difficult to differentiate between pelvic conditions and the 4 marked types of appendicitis: 2 irritative lesions and 2 infective lesions. The leading diagnostic point differentiating between any form of chronic appendicitis and pelvic conditions lies in the fact that the right sympathetic lumbar ganglion only is hyperesthetic on pressure; whereas in any chronic pelvic irritation or infection, both right and left ganglia hyperesthetic. There is no direct nerve connection between the appendix and the ganglion in question. R. T. Morris (*Trans. Amer. Med. Assoc.*; *N. Y. Med. Jour.*, June 30, 1917).

By the use of the proper X-ray methods of examination the appendix can be studied very advantageously in most cases. The patient should be prepared by a dose of castor oil [Never in an acute case. Ed.] before the opaque meal. The best opaque meal is 425 c.c. ($\frac{3}{4}$ pint) of buttermilk with 150 Gm. (5 ounces) of barium, or less, depending upon the subject's build. The following points deserve special stress: 1. Manipulation and careful screening are necessary to find the appendix, to determine its tenderness, and to reveal its mobility and movements. 2. Several plates must be taken as they, alone, reveal the chief features which must be studied. 3. The patient should be either supine or in the semilateral position. 4. The positions of the parts are first determined by manipulation with the gloved hand, while the wooden spoon is used for the

later manipulations because it is not opaque and plates can be taken when the appendix is brought into clear view. 5. The ileum and cecum can usually be moved about to give the best exposures of the appendix. 6. If the appendix be behind the cecum a semilateral view may reveal it. 7. The end of the ileum and appendix should be shown filled at the same time when possible. 8. Movements must be very gentle, or must not be made, when there is pain, tenderness, or inflammation of the appendix. 9. A Coolidge tube should be used throughout, with a 2 millimeter aluminum screen. 10. Where the appendix fills in part only, or empties before it has completely filled and the case is doubtful, the usual dose of barium should be divided and given in a succession of meals. By a careful perfection of the technique the appendix can be revealed and studied in more than 80 per cent. of all cases. The details of the findings in both normal and diseased appendices are given at length and the authors summarize their observations by saying that the normal organ fills and empties at about the same time as the cecum; that in young people it may fill and empty repeatedly, the cecum remaining full; and that the best views are to be secured from 12 to 14 hours after the opaque meal. The determination of whether the appendix is, or has been diseased demands attention to its filling and emptying, its shape, and mobility, to the presence or absence of concretions, its position, and to the presence of hyperactivity, spasm, and tenderness. Continued contractions and spasm accompany active inflammation and, while the presence of a tender point is of value, it requires care in its interpretation. The direct X-ray examination of the appendix is of great aid in the diagnosis of cases of chronic appendicitis. In a series of 36 cases in which the X-ray and operative findings were compared the diagnosis was verified at operation in all. Spriggs and Marxer (*Lancet*, Jan. 18, 1919).

The general health and nutrition are usually impaired in these cases, particularly if the intervals between the attacks grow shorter. More or less marked neurasthenia, with coldness of the extremities, irritability, moroseness, and mental apathy, is usually present, owing, doubtless, to the anxiety which the disorder inspires. Stubborn constipation, more or less headache and vertigo, anorexia, a disagreeable "bilious" taste in the mouth, and "bad breath" are commonly complained of, the tongue, especially at its base, being often thickly furred. A peculiar pasty or bloated appearance of the face is also noticeable in some cases.

Appendiceal dyspepsia, previously referred to, and due, according to Moynihan, to exaggerated activity of the pylorus, is aggravated by gastrointestinal autointoxication through the intermediary of the appendiceal disorder, and disappears when the appendix is removed.

Pain chiefly in right lower quadrant, if unassociated with attacks of epigastric pain and nausea, is seldom due to the appendix; before diagnosing chronic appendicitis every other possible condition should be excluded. Stanton (*N. Y. State Jour. of Med.*, Oct., 1911).

In visceroptosis or neurasthenia sometimes acute appendicitis is simulated, but as a rule the condition is mistaken for chronic appendicitis. In this type of patient, there is no true abdominal rigidity, and the abdominal pain will decrease or disappear when the patient lies down. This last point is all important in differentiating between true and false appendicitis. Archibald MacLaren (*Annals of Surg.*, Nov., 1916).

Tenderness is the most important and most constant symptom. It may be elicited by the slightest palpation and is always definitely located over the appendix. Rigidity depends

largely upon the degree of tenderness. Slight tenderness will bring out no rigidity except the sudden spasmodic contraction at the moment of pain. Gastro-intestinal disturbances appear in diverse forms and are usually the cause of the patient's consulting a physician. G. D. J. Griffin (Ills. Med. Jour., xxxi, 403, 1917).

The writer observed 3 cases in which the regurgitation of food was the most annoying and prominent symptom. The appendicitis was of the chronic type. There were no very acute attacks, only 1 patient had an acute attack. Constipation was a marked symptom in 1 case notwithstanding the pericolic condition, and all of the patients enjoyed very good health. All of the patients were found to have a pericolic membrane, the appendix being bound down by fibrous tissue. Nifong (Mo. State Med. Assoc. Jour., Nov., 1920).

In hypochondriacs and hysterical subjects both acute and chronic appendicitis are sometimes suggested by symptoms recalling the latter condition, the hyperesthesia and pain in the right iliac fossa being especially marked. But a careful study of the history and antecedents of such cases, absence of tenderness when the patient's attention is attracted elsewhere, and of the doughy mass in the region of the appendix usually serve to indicate the true nature of the case.

To facilitate the diagnosis of chronic appendicitis the writer tried to *ascertain the lower, outer and inner borders of the cecum*, usually distended with gas by *percussion*; he estimates from this the position of the appendix, and finds out whether there is tenderness at that point. Where mapping out the cecum by percussion is not possible, he places the thumb at the junction of the right edge of the rectus muscle and umbilicospinal line, and, with it pointing toward the ensiform, sinks it in about halfway to the back of the abdominal cavity; next

he swings it to the right of the patient at a right angle to the line of previous pressure, thus *pinching the appendix against unyielding structures and eliciting tenderness* if it be diseased. If this test is negative, he repeats it $\frac{1}{2}$ inch lower, and tests again until the brim of the pelvis has been almost reached. Control is made by pressure on the left side. Bassler (Amer. Jour. Med. Sci., Aug., 1913).

The writer works the flexed fingers of the right hand, between the outer wall of the cecum and the abdominal wall; by extending them he then tries to push the cecum toward the midline. In chronic appendicitis this causes pain. Rutkevitch (Roussky Vrach, Mar. 21, 1915).

Bastedo's method of eliciting tenderness over McBurney's point by distention of the colon by means of an atomizer bulb, pain and tenderness occurring at that point in the presence of chronic appendicitis, was tried by the writer in 40 cases of intra-abdominal lesions. Practically in every case of chronic appendicitis the Bastedo sign was present, whereas it proved negative in the other conditions. Jacob Rosenbloom (Surg., Gynec. and Obstet., Nov., 1916).

Two signs belonging to the sympathetic and autonomic nervous system are of great importance in making a differential diagnosis between chronic appendicitis and other affections of the abdomen and pelvis. They do not occur in acute appendicitis. Chronic irritation of the appendix excites the second and third right sympathetic lumbar ganglia, the fused ganglion, rendering it hyperesthetic. Deep pressure upon the abdomen about $1\frac{1}{2}$ inches to the right of the navel and a trifle caudad evokes this hyperesthetic point. The second sign consists in permanent distention of the ascending colon. It is called the *cider barrel sign*. Percussion on the left side of the patient's abdomen gives a note reminding one of the outlines of such a barrel in October (full) for instance, while percussion on the right side of the patient's ab-

domen gives a note suggestive of the cider barrel only in March. R. T. Morris (Med. Rec., Jan. 11, 1919).

The ulcerative form with its attending danger of perforation may be suspected when a tumor is felt in the interval, and especially when the tumor has increased in size during the access.

Appendicitis and chronic colitis may occur as a complication of gastric ulcer. The former is frequent, the patient giving a history of previous attacks of appendicitis. In some instances the symptoms of the latter predominate, and the ulcer fails to respond to treatment until appendectomy is performed. Occasionally even this operations fails to procure relief, but this occurs under treatment for the ulcer. At times the appendiceal symptoms are due to displacement of the pylorus to the region of the appendix. This is revealed by an X-ray examination. Mathieu (Gaz. des Hôp., June 4, 1914).

While Lane's iliac band may cause symptoms almost indistinguishable from those of chronic appendicitis, its frequency and especially that of the symptoms from it have been greatly exaggerated. Jackson's pericolic membrane may also cause these symptoms because of the associated abnormal mobility of the intestine which may lead to torsion and stasis. Mobile proximal colon may alone give rise to similar symptoms, as may also inflammatory bands and adhesions. The commonest condition simulating chronic appendicitis, however, is right-sided chronic tubal and ovarian disease. In many of these cases an etiological diagnosis is practically impossible. John Morley (Lancet, Jan. 9, 1915).

The large majority of the attacks are due to any cause which may awaken the latent catarrhal process resulting from a previous attack treated medically. The pathological characters are the same as in the acute form, except in the fact that

adhesions are likely to be found if anything but a very mild attack has previously occurred.

In an analysis of 100 cases of obliterative chronic appendicitis operated upon by Deaver the writer found that appendicular sclerosis and its terminal stage, appendicular obliteration, differ pathologically and clinically from chronic active appendicitis. In the latter there is either a persistent low-grade infection, or recurring attacks separated by intervals of latency. In the former, no active or latent inflammatory process is present, but merely the end-results of such a process. With appendicular obliteration there are 3 types of symptoms: (1) *reflex*, due to irritation of the nervous mechanism of the appendix, the "dyspeptic" type of appendix; (2) *local*, due to mesenteric and peritoneal contraction, and inflammatory bands or adhesions affecting the appendix, cecum, ileum, or ascending colon; (3) *consecutive* symptoms, general and local, consequent upon disturbed function of the ileocecal region. Simple appendectomy avails for reflex symptoms, but in local and consecutive symptoms only insofar as the operation permanently frees symptom-producing contractions, sclerosis, or adhesions. D. B. Pfeiffer (Annals of Surg., Apr., 1915).

Chronic *appendicitis* is extremely frequent. The term is used by the writer to embrace a host of conditions, many of which are not inflammatory, although in part of inflammatory origin. Purely non-inflammatory are calculus appendices, some of which show mechanical ulcerations and simple constricted appendices. All of these kinds of pseudo-appendicitis cause a syndrome like that of the actual disease, and may require operative treatment. Naturally they are much less deadly than the true disease. In the wide sense of the term the "chronic appendix" is of such incidence as to be well nigh universal. This is apparent to every

laparotomist, and is perhaps the chief reason for perfunctory or routine extirpation of the organ. It is exceptional for the gynecologist to find a normal appendix in his female patients. Men no doubt suffer equally, although less obviously. Children suffer much less than adults. The appendix is a lymphatic, spongy structure, which can be infected by the blood or lymph route, as well as by the intestine. It is fully as vulnerable as the tonsil. Faure (*Presse méd.*, June 28, 1917).

X-ray and fluoroscopic examination facilitate the diagnosis in a large proportion of cases, particularly with the aid of barium meals.

The kinked and adherent appendix is shown by the X-rays. In cases of Lane kink one can demonstrate the fixed and distended terminal loop of ileum. In cases of Jackson's membrane one can show the effect of the adhesions under the fluoroscope, as well as the presence of a characteristic mechanism of filling. Various adhesions in this region from old inflammatory disease or congenital anomaly can be similarly shown. Cecum mobile and left-sided appendicitis can readily be demonstrated. Georgé and Gerber (*Boston Med. and Surg. Jour.*, Oct. 9, 1913).

X-ray examination obviates some errors in the diagnosis of chronic appendicitis. Fluoroscopic examination is the most satisfactory, visualization of the appendix being secured preferably with an opaque meal. If the appendical lumen be not patent, the appendix may of course not be demonstrable. M. J. Hubeny (*Ills. Med. Jour.*, xxix, 109, 1916).

A careful study of all cases diagnosed as chronic appendicitis is necessary, including use of the X-ray. The symptoms of chronic appendicitis and cecal disease are often very similar. Proper treatment for chronic intestinal toxemia clears up symptoms resembling chronic appendicitis. Autogenous colon vaccine should be tried in every case. The internist should

be always on the guard for appendicitis in every case of chronic intestinal toxemia. G. Reese Satterlee (*Amer. Therap. Soc.; Med. Rec.*, Sept. 23, 1916).

Quoting F. G. Connell, the writer states that out of 212 patients operated upon for chronic appendicitis, 87, or 41 per cent., were not relieved of their symptoms. By the fluoroscopic study of the barium-filled colon, it is possible to determine accurately the point of tenderness and pain as to whether it involves the ileocecal region and appendix or the cecum or some point distant from the appendix. The mobility of the cecum is absolutely determined, as is also the question of visceroptosis, spastic colitis, or ileac stasis. The X-ray method of diagnosing a chronic appendix is the most reliable. R. T. Pettit (*Arch. Radiol. and Electrotherap.*, xxi, 345, 1917).

PROGNOSIS.—The chances that a first or second attack of acute catarrhal appendicitis will be renewed are about 77 per cent.; but when a fourth or a fifth attack has occurred, the probability is very great that more will follow and ultimately end fatally, unless operation is performed.

After the patient has gone through an acute attack safely, and the characteristic tumor indicating an acute suppurative process is felt, a circumscribed peritonitis, rather than a general suppurative one, is likely to occur if another attack takes place.

TREATMENT.—Appendectomy is indicated at the first relapse, and when a tumor is present during the interval, the presence of septic accumulation, ulceration, or perforation being likely. It may be performed during a period of quiescence in the manner described in the preceding pages.

All patients with chronically diseased appendices should be subjected to operation immediately the diag-

nosis is made, provided there are no constitutional contraindications. Such patients, with few exceptions, if not operated upon, suffer from chronic indigestion, dyspepsia, chronic intestinal stasis, neurasthenia, etc., and sooner or later have an acute attack. The only valid contraindications are severe pulmonary disease, an uncompensated heart lesion, and in general those lowered states of vitality the results of constitutional disease, which would render inadvisable any operative intervention. The responsibility for delay in operation in the case of chronic appendicitis should be assumed by the patient to whom a clear statement of the hazards of this condition should be given by the medical or surgical attendant. Under no circumstances should he be permitted to believe that any form of medical treatment can prevent an attack, or cure it if it occurs. J. B. Deaver (N. Y. Med. Jour., Feb. 10, 1912).

In 70 cases of chronic appendicitis traced subsequently, 70 per cent. of the patients had been cured by the operation, while relief had been given in 30 per cent. In the latter the appendix was diseased only as part of a more general disease of the large intestine. The symptoms were pains in the right iliac fossa, radiating to other parts, with disturbances in defecation, tenderness in the right iliac fossa, resistance, and röntgenoscopic delay in the digestion in the cecum. The pains constituted rather a sense of oppression or discomfort than the boring or stabbing pain of appendicitis. With colitis the pains spread over the entire abdomen and are more constant. Exacerbation from physical effort or menstruation rather suggests general bowel trouble, while constant tenderness at McBurney's point speaks for chronic appendicitis. In the latter, however, especially the recurrent form, there is frequently no tender point anywhere. Resistance in the ileosacral region suggests participation of the colon, as do also constipation, intestinal fermentation

and mucus in the stools. Colitis can be either the consequence or cause of chronic appendicitis. If improvement occurs under physical and dietetic measures, appendicitis can generally be excluded. A tendency to nervous disturbances also speaks against localized appendicitis. Krecke (Münch. med. Woch., Mar. 18, 1913).

Chronic appendicitis in women is usually accompanied by cystic degeneration of the ovaries. The symptomatology due to the ovaritis is much the same as the symptomatology of chronic appendicitis. Operation should be aimed toward the appendix and the ovaries, distinguishing the two different conditions involved in the ovaritis. R. S. Gomez (Rev. argent. de obst. y. ginec., Buenos Aires, i, 157, 1917).

When operative procedures cannot for one reason or another be resorted to, **dietetic and medical measures** should be resorted to, to limit as much as possible the morbid process. Red meats should not be allowed more than once daily, and a **farinaceous, vegetable, and milk diet** favored. Complete abstention from meats is sometimes necessary. Where any degree of gastric catarrh exists, **gastric lavage** with a solution of **sodium carbonate** (1 dram—4 Gm.—to the quart) every other day, with **bismuth** (10 grains—0.6 Gm.) twenty minutes before meals, are indicated. A **flannel bandage** so adjusted as to pass over the region of the appendix serves to protect the abdomen from sudden chilling, and is an excellent prophylactic measure.

The bowels should be kept free by the use of mild **saline aperients**, with **magnesia** as main active agent.

In appendicular dyspepsia the medical treatment, pending operation, consists in regulation of the **diet**, **disinfection of the intestines**, and modification of the general neuropathic condition. Nitrogenous food should be reduced,

all excitement and indigestible substances forbidden, and a **vegetable** diet predominate. Disinfection of the intestines may be produced by the periodical use of **laxatives** and **intestinal lavage**. To improve the general and gastric neuropathic condition, general and local **hydrotherapy** may be used, together with **calcium bromide**, **belladonna**, **valerian**, and **codeine**. Fouchard and Salignat (*Presse méd.*, May 25, 1907).

In the appendicitis occurring in conjunction with gastric ulcer the writer obtained the best results with **bismuth subcarbonate** 5 drams (20 Gm.) and **magnesium oxide** 75 grains (5 Gm.) daily, the first being increased if pain is the more prominent symptom, while the magnesia is increased if constipation is the more troublesome. This treatment is also indicated when chronic colitis complicates the case. Mathieu (*Gaz. des Hôp.*, June 4, 1914).

AFTER-TREATMENT OF THE VARIOUS FORMS. — The patient should not leave his bed until the subsidence of all trace of inflammation and proper healing of the wound have taken place, namely: from ten days to two weeks. In cases complicated with drainage a longer period may be necessary.

The *postsurgical treatment* is important and should be conducted with great care. The stomach should be given complete rest for twelve hours, **cracked ice** and **water** being allowed in moderation. After that, **liquid food**, beginning with **peptonized milk**, if there is any tendency to nausea or vomiting, may be given. To keep the intestinal tract as clear as possible, a daily **injection of lukewarm soap and water** is sufficient. A mild cathartic may be given after third day. The patient should lie on his back the first two days, then begin to change his positions in bed, if he desires,

without violence. **Opium** should be given in small doses if there is much pain.

The outside dressing should be changed every day at first, and the packing removed on the fourth or fifth day after operation. In cases of limited abscess the drains should be started earlier. This should be done with great care and the cavity cleansed by dry sponging, no fluids being introduced into the wound. The wound is then repacked and left so three days, and renewed when necessary. As the packing is renewed from time to time, it should be reduced in size at each sitting, to permit the wound to heal from the bottom.

The plan of **Murphy proctoclysis**, already described, should be followed in all cases where any but the slightest grade of peritonitis is encountered.

Certain bad results following operations for chronic appendicitis were studied by the writer in 355 cases in the New York Hospital. Patients with somewhat indefinite symptoms, the vagatonics, are frequently subjected to operation needlessly and recklessly. Bad results fell from 28 per cent. in 1913 to 11 per cent. during the last 6 months of 1919, in proportion as the small inguinal incision was abandoned for a larger incision. A large incision allows of a more complete examination, many bad results following appendectomy being due to failure to look for and recognize other conditions coincident with the appendicitis. The improvement in the statistics is also in a large measure attributable to more thorough work in looking for complications, especially in women. A comprehensive total history and a thorough physical examination is essential. C. L. Gibson (*Trans. Acad. of Med.; Med. Rec.*, Feb. 28, 1920).

WILLIAM B. COLEY,
New York.

ARISTOL.—This is an iodine compound used locally to enhance healing processes, prepared by adding a solution of iodized potassium iodide to an aqueous solution of sodium hydrate containing thymol. The dried precipitate, constituting a dithymol diiodide, occurs in the form of a reddish-brown, almost tasteless powder having an iodine-like odor and containing 45 per cent. of this element. It is readily soluble in collodion, ether, and chloroform, and slightly so in alcohol, but is insoluble in water and glycerin. The fact, however, that it is employed locally annuls these disadvantages.

PREPARATIONS.—Aristol may be used in the form of a *powder*; it adheres to the skin and if the latter is broken does not cause irritation. It does not have any appreciable toxic effects if absorbed. It is not very active as an antiseptic, and its germicidal action is limited, but it prevents infection and promotes very effectively absorption and cicatrization.

Aristol may be employed in the form of *ointment*, wax and lanolin being best fitted for this purpose. It is best used in strengths ranging between 5 and 20 per cent. It may also be employed, dissolved in lanolin, as an *oily spray* for the respiratory passages, a 5 per cent. solution being advantageous, with an oil atomizer.

THERAPEUTICS.—The value of aristol is especially noticeable in **ulcers** of various kinds, such as those due to **adenitis**, **chilblains**, **boils**, **varicose veins**, after careful disinfection with some antiseptic solution. This applies also to **burns** and **scalds** of the second or third degree. In any of these the powder or ointment can be used to advantage. In **vaccination ulcers**, I have seen it act with marked rapidity where other measures had failed. It favors the healing of superficial **wounds**; lacerations of the scalp, for instance, are made to heal with great rapidity. It is also efficient in **hyperidrosis** when used as a dusting powder. In **syphilitic ulcers**, **chancroids**, **buboes**, and venereal ulcerative processes in general, it has been found as effective as in simple ulcers. Aristol has given good results in indolent **corneal ulceration** when applied as a powder with a camel's hair pencil. The 5 per cent. ointment is useful in **blepharitis**. Pow-

dered aristol blown over the mucous surfaces is helpful in **ozena** and **chronic rhinitis**, as well as in ulcerations of the genital organs, **uterine erosions**, **endometritis**, and **eczema vulvæ**. S.

ARNICA.—This is the plant *Arnica Montana*, or leopard's bane, a perennial of the natural order Compositæ, indigenous to the mountains of northern Europe and Siberia, as well as to the western United States. The flowers are large and orange yellow, and there is a small, curved rhizome with several rootlets. The dried flower-heads are official. The plant contains an ammoniacal alkaloidal principle, *trimethylamine* $[N(CH_3)_3]$, which is doubtless the active ingredient. It contains also *arnicin*, inulin, capronic and caprylic acids, tannin, mucilage, resins, and two essential oils.

PREPARATIONS.—*Tinctura arnica*, a tincture of 20 per cent. strength, made from arnica flowers.

A tincture of arnica root has also been prepared and used.

The internal dose of either preparation is 10 to 30 minims (0.6 to 2.0 c.c.), though arnica is used chiefly externally.

PHYSIOLOGICAL ACTION.—**Locally** applied, arnica acts as a *stimulant* and often a decided irritant. In case of a delicate skin, where it may produce not only burning and irritation, but even decided skin lesions. **Internally** it slows the heart, but seems to raise arterial pressure slightly and stimulate the vagus nerves; it also increases the action of the skin and kidneys. In large doses it is emetic and cathartic, causes great muscular weakness, a rapid pulse, and, if the dose be excessive, collapse. It appears to be eliminated by the skin and kidneys.

THERAPEUTIC USES.—Arnica has been used internally as an antipyretic and stimulant in **typhus** and **typhoid fevers**, as well as in **concussion of the brain**, **delirium tremens**, **rheumatism**, **epistaxis**, **chronic dysentery**, and **paralysis of the bladder**. The drug is seldom used internally nowadays, but externally is a popular remedy among the laity for **sprains** and **bruises**. When thus employed its irritating qualities should be borne in mind, especially in patients with tender skins. W.

ARSACETIN. See ATOXYL.

ARSENIC (*Arsenum*).—Metallic arsenic appears as a steel-gray, lustrous, brittle mass, which is odorless and tasteless. When heated to 140° C. or over, it emits an odor of garlic; the metal is volatilized, and becomes more or less rapidly oxidized, according to the temperature, to form arsenic trioxide, As_2O_3 . The latter is the so-called "arsenic" used in medicine,—also known as white arsenic, arsenous oxide, arsenous anhydride, ratsbane, and, incorrectly, as arsenious acid.

Arsenic is prepared commercially from the native ore by a process of roasting and sublimation.

PROPERTIES.—When freshly sublimated, arsenic trioxide appears as an amorphous, vitreous, "glassy" mass. Upon absorption of moisture from the air, white, opaque crystals are formed, which constitute the "porcelain-like" variety of the oxide of arsenic. As generally dispensed, after being ground in a mortar, the product consists of a mixture of small amorphous particles and crystals, odorless, practically tasteless, and having the specific gravity 3.7. At ordinary temperatures arsenic trioxide dissolves but slowly in water, the glassy variety requiring 30 parts of the latter for solution, and the crystalline variety 100 parts. In boiling water, however, arsenic trioxide dissolves to the extent of 1 in 15 parts. Its solution is accompanied by the formation of arsenous or arsenious acid (H_3AsO_3), of which arsenic trioxide is the anhydride. In alcohol, arsenic trioxide is but slightly soluble; in hydrochloric acid and solutions of alkalis or of carbonates of the alkali metals, how-

ever, it is freely soluble. Glycerin dissolves it to the extent of 1 part in 5; the glassy variety alone dissolves in turpentine oil.

PREPARATIONS AND DOSE.—

The official preparations containing arsenic are as follows:—

Arseni trioxidum (arsenic trioxide; "arsenious acid;" white arsenic); dose, $\frac{1}{60}$ to $\frac{1}{12}$ grain (0.001 to 0.005 gram).

Liquor acidi arsenosi, containing 1 per cent. of arsenic trioxide; dose, 1 to 10 minims (0.06 to 0.6 c.c.).

Liquor potassii arsenitis (Fowler's solution), made from 1 part of arsenic trioxide, 2 parts of potassium bicarbonate, and 3 parts of compound tincture of lavender, with enough water to make 100 parts; dose, 1 to 10 minims (0.06 to 0.6 c.c.).

Liquor sodii arsenatis, containing 1 per cent. of exsiccated sodium arsenate; dose, 1 to 10 minims (0.06 to 0.6 c.c.).

Liquor arseni et hydrargyri iodidi (Donovan's solution), containing 1 per cent. each of arsenous iodide and red mercuric iodide; dose, 1 to 5 minims (0.06 to 0.3 c.c.).

Arseni iodidum (arsenous iodide), a reddish, crystalline powder, soluble with partial decomposition in about 12 parts of water, and in about 28 parts of alcohol; it is required to contain not less than 82.7 per cent. of iodine, together with 16.3 per cent. of metallic arsenic; dose, $\frac{1}{10}$ grain (0.006 gram).

Sodii arsenas (sodium arsenate), occurring in colorless crystals, which are soluble in 1.2 parts of water; dose, $\frac{1}{10}$ grain (0.006 gram).

Sodii arsenas exsiccatus (dried sodium arsenate), an amorphous white

powder, soluble in 3 parts of water and very sparingly soluble in alcohol; it is nearly twice as strong as the preceding preparation; dose, $\frac{1}{20}$ grain (0.003 gram).

Mentioned in the National Formulary are the following preparations of arsenic:—

Liquor sodii arsenatis, Pearson (Pearson's solution), containing about $\frac{1}{6}$ per cent. of crystalline sodium arsenate and being therefore much weaker than the official solution of sodium arsenate; dose, 5 to 30 minims (0.3 to 2.0 c.c.).

Liquor potassii arsenatis et bromidi (Clemen's solution), made by boiling arsenic trioxide and potassium carbonate together in water, adding pure bromine, and shaking the mixture repeatedly until it remains clear. Contains 1 per cent. of arsenic trioxide and 2 per cent. of bromine. Dose, 1 to 5 minims (0.06 to 0.3 c.c.).

Liquor auri et arseni bromidi (solution of bromide of gold and arsenic). Each 10 minims (0.6 c.c.) contain $\frac{1}{32}$ grain (0.002 gram) of tribromide of gold and the equivalent of $\frac{1}{13}$ grain (0.005 gram) of tribromide of arsenic. Dose, 3 minims (0.2 c.c.).

Arsenic is also contained in the following organic compounds: Cacodylic acid (*q.v.*) and cacodylates, atoxyl (*q.v.*), soamin (*v.* Atoxyl), arsacetin (*v.* Atoxyl), arsenophenylglycine (*v.* Atoxyl), arrhenal (*v.* Cacodylic acid), and dioxydiamidoarsenobenzol (*q.v.*).

MODES OF ADMINISTRATION.—Where arsenic is to be given internally in liquid form, Fowler's solution (liquor potassii arsenitis) or the liquor sodii arsenatis may be used; either preparation should be given after meals, freely diluted in

water, as the drug is irritating to mucous membranes. For administration in pill form, the trioxide is well adapted. The drug is generally given either in ascending doses, beginning with small amounts and then gradually increasing; or, less frequently, in descending doses, beginning with the maximal amount and gradually decreasing. The first of these methods is the safer, since in some patients intolerance even to moderate doses of arsenic is encountered. For administration of full doses in cases where the gastrointestinal tract is irritable or has rebelled, the subcutaneous method is available. A good preparation of Fowler's solution, containing no free arsenous acid, diluted with distilled water, may be employed for this purpose, provided strict aseptic precautions be taken; the preference is now given, however, to the less irritating organic combinations of arsenic, especially the cacodylates, *q.v.* Moyer, in 28 cases of chorea, used a solution of pure anhydrous sodium arsenate with satisfactory results. Rectal administration of arsenic has been tried out and recommended by Renaut, who gave injections of $\frac{1}{20}$ grain (0.003 Gm.) of the trioxide in $1\frac{1}{4}$ drams (5 c.c.) of water three times daily in early cases of tuberculosis and in diabetes mellitus and exophthalmic goiter. He found that this treatment could be continued for months without causing gastric disturbance. Where rectal irritation appeared, a few drops of laudanum were added to the solution given.

Arsenic is well borne by children, and may be given to them, if necessary, in doses relatively larger than

are generally tolerated by adults. At all ages, however, it is desirable, owing to the fact that arsenic tends to accumulate in certain of the viscera, to suspend its administration for a week or ten days after it has been given steadily for a period of two to eight weeks (according to the doses given).

INCOMPATIBILITIES.—Liquid arsenical preparations are incompatible with most of the metallic salts, including especially those of silver, iron, copper, calcium, and magnesium. In prescribing the arsenical liquors, care should be taken to avoid chemical incompatibility by observing the reaction of the preparations with which they are to be combined: In acid solutions the liquor acidi arsenosi should be used, in alkaline solutions the liquor potassii arsenitis, and in neutral solutions the liquor sodii arsenatis.

CONTRAINDICATIONS. — Arsenic is contraindicated in acute skin diseases with local discomfort and evidences of an active inflammatory process. In inflammatory affections of the gastrointestinal tract its use is also, in general, unwise, though in cases presenting vomiting as the only or most prominent symptom its administration is permissible and even, it is claimed, sometimes beneficial. In acute infections with fever,—an exception being sometimes made in the case of malaria,—arsenic is also considered harmful.

Symptoms of beginning intolerance such as anorexia, digestive disturbance, conjunctival irritation, and swelling of the eyelids, should be watched for in patients taking arsenic, and their appearance be taken as a signal to interrupt for a time the use

of the remedy, or, at least, to stop the progressive increase in the dosage.

PHYSIOLOGICAL ACTION.—

Local Effects.—Arsenic preparations act as slow caustics. Brief contact of arsenicals with the skin does not affect the latter, but their more prolonged presence, even in relatively high dilution, results in local hyperemia and the production of a vesicular or pustular eruption. It differs from most other caustics in affecting especially the living cells, dead tissues remaining uninfluenced. The pain produced as a result of its caustic effect is slight in comparison with that of strong acids and alkalies. Correspondingly, the subcutaneous injection of arsenic compounds, uncombined with other irritants, does not give rise to any great degree of pain. Mucous membranes, however, seem to be more sensitive to its irritating action, considerable discomfort, as well as destruction of tissue, being produced.

General Effects.—*Nervous System.*—Small doses of arsenic repeatedly given may be said to stimulate the nervous system as a whole. Some direct effect of the drug on the nervous tissue is believed to be exerted, though, as is the case with most other drugs, no definite information is as yet available concerning the exact chemical or physicochemical changes it induces. A continuance of the stimulating effect, as in chronic arsenic poisoning, results in inflammation of the peripheral nerve tissues, *i.e.*, neuritis, which involves the possibility of ultimate degeneration and loss of function.

Where the drug is taken in larger amounts, the stimulation produced is more sudden and less likely to lead to inflammation. The secondary effect is

then a depression or paralysis of function more immediate than that succeeding inflammation, and which may, through involvement of the medulla, with its centers of respiration and vasomotor action, produce death by respiratory failure—the common termination in fatal acute arsenic poisoning. It should be borne in mind that even a single dose of arsenic, poisonous but not large enough to cause prompt death, may produce neuritis.

Examining the effects of acutely toxic doses of arsenic on the nervous system more closely, we find that the sensory apparatus is generally the earliest affected. The frog poisoned with arsenic exhibits a descending paralysis the successive manifestations of which are loss of spontaneous movements, insensibility to mechanical and chemical stimuli,—showing paralysis of sensation,—and finally motor paralysis. That ligation of the artery to a limb before injection of arsenic—thus preventing the drug from reaching the extremity after its absorption—does not prevent the loss of sensation and motile power in that limb, shows that the paralyzing effect is produced on the centers rather than at the periphery.

Circulation.—The chief circulatory effect of arsenic is a lowering of the tonicity in, or actual paralysis of, the walls of the capillary vessels, especially those of the gastrointestinal tract. The improved state of nutrition brought about by “tonic” doses of arsenic may in part be the result of a relative hyperemia and consequent greater functional activity of the alimentary organs. In any doses but the smallest, however, the hyperemia verges upon or actually amounts to an inflammation; the permeability of the dilated capillaries is so increased that a large amount of fluid

escapes from them, lifting up the superficial mucous layers of the gut from the subjacent tissues, and the result is a profuse, watery diarrhea containing varying amounts of shreds of the mucous membrane and extravasated red blood-cells. This action on the capillary vessels is believed to be exerted directly on them,—not through the intermediary of any centers of vasomotor regulation. If a large dose of arsenic be injected intravenously into a mammal the vascular dilatation produced is so extensive that a marked fall in the blood-pressure occurs. Pronounced hyperemia of the gastrointestinal tract is also seen, indicating that the low pressure is due, at least in major part, to recession of blood into the splanchnic vascular area.

Though not as yet experimentally proven, it appears reasonably certain that the edema witnessed in chronic arsenic poisoning is due to dilatation and increased permeability of the capillaries of the parts concerned. This is in agreement with the fact, mentioned by Sollmann, that intravenous injection of large amounts of salt solution will produce edema in animals subjected to arsenic, whereas in the normal animal it will not.

Upon the heart arsenic clearly does not possess the marked depressant effect of the closely allied metal, antimony. Massive doses of the former, however, do seem to weaken the heart sufficiently to prove a contributory factor in the fall of blood-pressure produced by intravenous injections of arsenic preparations. Whether the vasomotor center is appreciably depressed by toxic doses of arsenic is not definitely known.

Respiration.—No significant effects upon the breathing are exerted by small

doses of arsenic taken by the mouth. Injected intravenously, arsenic preparations tend at first to increase the respiratory rate. Lethal doses arrest the respiration before cardiac arrest occurs; this does not necessarily indicate, however, a direct effect of the drug upon the centers in the medulla, which may be influenced indirectly through the circulatory changes.

Alimentary Tract.—Whether taken by mouth or injected under the skin, arsenic exerts its earliest effects upon the intestinal tract, causing, as has already been said, a dilatation of the capillary vessels corresponding in its extent with the dose taken. Subcutaneous injection of the drug induces this effect just as readily as oral ingestion; hence it is evident that the action of arsenic is not, as formerly thought, that of a locally acting, corrosive agent,—especially in view of the fact that the proportion of arsenic excreted from the general system into the alimentary tract is very small (Sollmann). The gastroenteritis produced by excessive amounts of arsenic differs from that of true corrosives in being accompanied by a profuse, serous diarrhea, owing to the greatly increased permeability of the dilated and paralyzed capillaries.

While vascular changes will account for most of the manifestations of arsenical action in the gastrointestinal tract, they fail to explain satisfactorily the cloudy swelling and fatty degeneration of the epithelium which may also be witnessed. The presence of an additional direct effect of arsenic on the cells, comparable to that of phosphorus, would thus seem to be indicated. This cellular effect is not limited to the alimentary tract, but involves other glandular and muscular organs.

Small doses of arsenic improve the

appetite and are credited with the power to enhance the digestive processes. Whether these effects are due to a mild vasodilator action or to a direct action on the cells is not known.

Skin.—Prolonged use of large doses of arsenic exerts a pronounced influence upon the skin. The growth of the epithelium is stimulated, causing the superficial layers to become thicker than normal. According to Jamieson, arsenic gives rise to hyperidrosis of the palms and soles by stimulating the sweat-glands, then to the formation of warty corns, and finally to a diffuse hyperkeratosis, associated with burning sensations. General pigmentation is also in some cases caused by arsenic, owing to the deposition of some dark-colored material—not an arsenic compound—in the dermis. Skin eruptions frequently occur in arsenic poisoning. In extreme cases, degeneration of the skin may ensue.

Arsenic does not combine with albumin and does not arrest cellular activity, but, on the contrary, it stimulates the protoplasm to greater activity. This stimulation, according to Binz, is due to the liberation of oxygen in the tissues. Arsenic forms two oxides, one with two atoms of oxygen more than the other. When As_2O_5 comes in contact with air, water, and organic matter, it is reduced to As_2O_3 , thus liberating two atoms of oxygen. This reduction takes place only where protoplasm is alive or dying. It will not occur in dead matter. Other elements have been found to have this same property of carrying separable, energetic atoms of oxygen; among these may be mentioned lead, phosphorus, antimony, bismuth, and nitrogen.

When oxygen is liberated slowly and in moderate quantities, the result is a formative tendency. This theory is borne out by the fact that if arsenic is fed to horses and sheep there is

improvement in the condition of the hide, as well as an increase in size. Giess found that by feeding arsenic to rabbits he could make them grow to enormous size. If, on the other hand, the respiratory process is accelerated and the oxygen is rapidly given and taken, the nutritive processes of the cells are hurried on beyond their power of endurance. The result then is exhaustion, degeneration, atrophy, and finally death of the tissue.

Epithelium shows an extraordinary affinity for arsenic. It is therefore natural to find a great variety of skin lesions in arsenic poisoning.

The drug is carried to the basal layer and passed on from cell to cell, being finally cast off in the desquamating scales and hairs. The changes produced are essentially nutritive, the tissues in the early stages presenting a condition of well-being. Under continued action, degeneration processes and deposit of pigment take place. Still later there is atrophy, and the epidermis may be very much reduced in thickness. In very advanced cases there is degeneration of the glands of the skin, the sweat- and oil- glands. Washburn (Wis. Med. Jour., Oct., 1911).

Blood.—It would seem established by clinical experience that in certain forms of anemia, such as progressive pernicious and posthemorrhagic anemias, arsenic tends to stimulate the formation of red blood-corpuscles. Under normal conditions, however, its effects, as observed in experimental work, are not such as would confirm this effect of arsenic. Thus Stockman and Charteris, investigating the changes produced by arsenic in the bone-marrow, observed merely an increase in the number of leucoblastic or leucocyte-producing cells, together with increased vascularity and atrophy of fat-cells. Stockman and Greig did not find any increase in the number of red cells or

hemoglobin percentage upon administering arsenic to normal animals. Bettman found in rabbits that slowly toxic amounts of arsenic caused the appearance of nucleated red blood-corpuscles in the blood, though the total number of erythrocytes and also the hemoglobin percentage were reduced. On the whole, the evidence concerning an effect of arsenic on the red cells may be said to be still inconclusive, though Bettman's findings would suggest that two processes are simultaneously at work, the one tending to destroy the mature corpuscles already present in the blood, and the other an effort—unsuccessful, it would appear—to replace those lacking by young, still nucleated cells.

Various authors have come to the conclusion that because arsenic seems to have no direct effect in increasing the production of red blood-corpuscles its beneficial results must come from its specific action on the parasites causing the disease for which it is given. In a series of experiments in which he has mixed arsenic in a suspension of blood-corpuscles, the writer shows that arsenous acid is fixed to the red blood-corpuscles, that this process takes place very rapidly, and, furthermore, that it protects these corpuscles against the hemolytic action of distilled water. He believes that in some way the arsenic affects the stroma of the red cells in the hemoglobin, but this stroma is known also to contain lecithin and cholesterin. J. A. Gunn (Brit. Med. Jour., July 18, 1908).

Arsenic, whether in the form of sodium arsenite or sodium arsenate, exerts on the red blood-corpuscles an action antagonistic to that of certain hemolytic agents. In a previous paper the writers pointed out that very dilute solutions of arsenous acid exert on the red blood-corpuscles *in vitro* a distinct protective action

against hemolysis by hypotonic saline solutions. In the later experiments, however, hemolytic agents of diverse nature were employed, namely, distilled water, cyclamin, and sodium glycocholate. These experiments account for the as yet imperfectly explained benefit which results from the medicinal administration of arsenic in pernicious anemia. Gunn and Feltham (Brit. Med. Jour., Jan. 21, 1911).

The examination of 123 cerebrospinal fluids collected at intervals ranging from 5 minutes to 23 hours after intravenous injection of from 0.3 to 0.6 Gm. (5 to 10 grains) of arsphenamin, 38 revealed appreciable amounts of arsenic. The largest found was 0.6 mg. of arsenous oxide in 10 c.c. The average amount was 0.18 mg. per c.c. The shortest interval at which arsenic was found was 30 minutes; the longest 2 hours. With successive injections, the fluids in general show progressively smaller amounts of arsenic for the same interval. Rieger and Solomon (Jour. Amer. Med. Assoc., July 6, 1918).

Nutrition and Metabolism.—Small doses of arsenic are frequently credited with the power to improve general nutrition. In young animals, growth appears to be stimulated by it. Though Stockman and Greig observed experimentally that only the development of the bones was favored, Gies, working with young rabbits, found that animals given very small amounts of arsenic showed greater body weight, with better muscular and adipose development, than their untreated fellows. Nitrogenous excretion, and also carbon-dioxide excretion, are somewhat diminished by small doses of arsenic, according to certain observers. Weiske claims that with arsenic a greater proportion of the food is taken up by the alimentary tract than normally, and that less protein destruction occurs in the tissues,

thus accounting for the favorable nutritive state resulting. It seems quite plausible that the first of these effects should result from a state of slight capillary dilatation in the gastrointestinal tract such as would probably be produced by moderate doses of arsenic, the various digestive functions, including absorption, being therefore better performed. The diminution of protein destruction in the tissues, however, is not by any means established; in fact, Sollmann considers it proven that so long as the amount of arsenic present does not interfere with the digestive processes, the excretion of nitrogen is increased.

The writer calls arsenic the digitalis of metabolism. In an experimental research on its action, he found that animals fed with arsenic developed much better in every respect than the controls from the same litter. That this better physical development includes the vital tissues and is not merely increased accumulation of fat is shown by the fact that the total tissues of the animals ground into a homogeneous mass, from which water and fat were extracted, showed a larger proportion of nitrogen in the arsenic animals than in the controls. He accepts this as evidence that the arsenic actually promotes the metabolism as digitalis promotes the action of the heart—laboratory research thus lumbering along to explain the facts observed by empiric observation generations ago. He fed dogs with arsenic over long periods; one of the dogs, a fox-terrier, he thinks, must be accorded the record for eating arsenic, as he took 0.5 Gm. of arsenic daily for two months and then 2.6 Gm. a day without harm, the arsenic feeding being kept up for over two years. Cloetta's further research, however, swept away the idea that the animal had become habituated to the drug, as it was proved that he merely had

ceased to absorb it. The lining of the alimentary canal had evidently become modified in such a way that it ceased to absorb the arsenic. This is probably the explanation for the resistance to arsenic acquired by trypanosomes in time and suggests the importance of supplementing salvarsan or other preparations of arsenic with mercury to which the spirochetes do not acquire resistance so soon. Cloetta (*Jour. Amer. Med. Assoc.*, from *Correspondenz-Blatt f. schweizer Aerzte*, July 20, 1911).

In poisoning by arsenic, distinct metabolic changes are to be observed. Nitrogenous metabolism is unmistakably increased, the amount of nitrogen passed in the urine being clearly augmented. A more or less characteristic effect is the rapid and complete disappearance of the glycogen from the liver. Sarcolactic acid is simultaneously formed and the alkalinity of the blood diminished. Glycosuria is no longer produced by Claude Bernard's puncture of the medulla in arsenic poisoning. Fatty degeneration of the epithelia, not only of the gastrointestinal tract, but also of the kidneys and liver, as well as of voluntary muscle tissue and that of the heart and vessels, also results. The phenomena resemble closely in most respects those of phosphorus poisoning, though not quite so pronounced. Jaundice may be an accompaniment of arsenic poisoning, owing to the changes produced in the liver.

Experimental findings that the kidneys of animals given lethal doses of arsenous acid, salvarsan, neosalvarsan, galyol, arsenophenylglycin, atoxyl, and arsacetin are separable into two extreme groups, the red and the pale kidneys, with transitional types in which the predominating changes ally them more closely with the one group or the other. In the group of red

kidney, congestion and hemorrhage are the dominant features of the arsenic action, while in the pale kidneys, the dominant lesion is tubular. Pearce and Brown (*Jour. Amer. Med. Assoc.*, Sept. 25, 1915).

ABSORPTION AND ELIMINATION.—Arsenic in inorganic combination is rapidly absorbed into the system, whatever be the mode of introduction. Even when it is applied to the intact skin, sufficient absorption may take place to induce poisoning. Organic preparations in which the element arsenic is not present in the form of an oxide, but is directly bound to carbon, as in arylarsonates, do not, however, exert their effects so promptly, as the arsenic has first to be oxidized through the agencies residing in the body tissues, probably into the form of an arsenite—before the familiar “arsenical” effects can be produced.

Scherbatscheff found through experiments on dogs that, even after therapeutic doses, arsenic remains for a long time in the organism, more especially in the brain and bones. After subcutaneous injection, the longest period noted by him was 160 days. After a short period of administration, it was found longest in the brain; but after more extended periods it was retained longest in the bones.

The elimination of arsenic is very gradual. Injected into the blood-stream, it is found rapidly to disappear from the latter and to become deposited in the tissues, in which it enters into a firm combination with the nucleins (Cushny). Repeated administration of the drug leads to its storage, not only in parenchymatous organs such as the liver, spleen, kidneys, and lungs, but also in the walls of the gastrointestinal tract and, to a certain extent, in the

muscles, bones, and nervous system. The excretion of arsenic takes place with the urine, feces, sweat, the epithelium shed from the skin, and, in nursing women, usually to a certain extent in the milk. Though its elimination begins within a few hours after exhibition, the major portion of a single dose of arsenic is not removed from the body for a number of days. According to Cushny, but one-fifth of the total amount of arsenic is lost with the urine and stools. A considerable proportion has been found to be very gradually eliminated in the superficial layers of the skin and in the hair, in which it may be detected for months after cessation of its use. In the urine of experimental animals it has been detected for as long a period as one hundred and sixty days after its administration had been stopped. It is excreted in the urine partly in organic combination.

Arsenic was found by Armand Gautier to be a normal constituent, in small amounts, of the human thyroid gland, and was also detected by him in the thymus, the brain, the skin, and in some instances in the hair, as well as in the mammary glands of a cow and in her milk. He did not find it, however, in various other tissues which he examined. Though Hödlmoser subsequently denied the presence of arsenic in any tissue of the normal body, Bertrand in 1903, in a series of experiments on animals, was able to confirm the findings of Gautier and even went farther, concluding that arsenic is a normal element of the living cell and is to be found in all animals and all organs.

The writer analyzed the tissues of certain animals, cetacea, birds, and fishes obtained in mid-Atlantic for arsenic. The object of obtaining the

animals from this source was to avoid the possibility of contamination from land sources. All the animals examined from vertebrata to sponges gave positive reactions to the test. The metal is not characteristic of certain groups of animals nor of certain organs. The thyroid gland has been stated to be especially rich in arsenic; other organs, for example, the liver, the muscles, and the testes have been stated to be free of traces of the metal. The method employed by the writer demonstrated a certain quantity in these tissues and in all others examined. Bertrand (*Annales de l'Inst. Pasteur*, Jan. 25, 1903).

The writers studied the ability of uterine glands to store arsenic as a cause of menstruation. Armand Gautier had demonstrated that the thyroïdal arsenic was discharged in the menstrual blood, where he found 0.28 milligramme to the kilo, the normal blood containing no arsenic. Hertoghe likewise showed that the premenstrual secretion sometimes discharged more arsenic than the menstrual blood, while the secretion after the menses never contained arsenic. The authors found that the arsenic discharged in the menstrual blood, does not come from the thyroid, but from uterine glands, which act specifically as repositories for arsenic, similarly to the thyroid. M. Ries and J. Ries (*Münch. med. Woch.*, May 14, 1912).

The view that arsenic is retained during pregnancy was confirmed by the writer in rabbits, human fetuses and the organs from pregnant cadavers, including two cases of eclampsia, and in some male cadavers. The organs of one young man who had succumbed to Banti's disease showed quite a large proportion of arsenic. It was positively known that he had taken no arsenic during eight months at least before his death. In all organs examined arsenic was found in amounts ranging from traces to considerable proportions. Frommer (*Arch. f. Gynäk.*, ciii, No. 2, 1914).

Acute Arsenic Poisoning.—This may arise in a variety of ways, arsenic being a constituent of many chemicals used in manufacturing and for household purposes. Paris green (copper acetoarsenite) and Scheele's green (copper arsenite), contained in rat poison and other parasitocides, have given rise to a number of cases of poisoning in human beings. Fly paper and fly powders contain arsenic in considerable quantities. Acute poisoning has been known to occur by inhalation of the fumes of candles colored with Scheele's green, from ingestion of candy containing arsenic, from application of arsenical plasters to skin cancers, from inhalation of arsine gas in chemical laboratories, from the use of cosmetics, etc. Haberda reported the case of a servant-girl who committed suicide by introducing white arsenic into the vagina.

The symptoms of acute arsenic poisoning, with the exception of a sweetish, metallic taste and a sensation of heat in the mouth, which may appear very promptly, come on usually in one-half to three-fourths hour after the ingestion of the drug, and consist at first of dysphagia, burning pain in the esophagus and stomach, and nausea. Later the pain increases, vomiting occurs, and a profuse, watery diarrhea sets in. Blood may appear in both vomitus and stools, but more characteristic of the latter is the appearance in them, after diarrhea has persisted for a short time, of small shreds of the intestinal mucous membrane which, together with the serous fluid issuing from the paralyzed and very permeable capillary vessels of the gastrointestinal walls, finally constitute almost the whole bulk of the dejecta, and bring them into the same category as the "rice-water" stools of cholera

Asiatica. The marked loss of fluid from the body induces an excessive thirst; the skin becomes pale and cold; the urine is scanty or suppressed, frequently albuminous in so far as it is secreted, and headache, giddiness, together with cramps in the limbs, may appear. A state of collapse, with the rapid, feeble pulse and dyspnea, is then seen, which may be ascribed either to insufficiency of blood-supply to or direct depression of the medullary centers, together with enfeeblement of the heart muscle owing to a toxic effect of the drug upon it. Coma and occasionally convulsions precede death.

In certain cases variations from the above description may occur. Symptoms of collapse may appear promptly and suddenly, and the poisoning run its course with but little pain and gastrointestinal disturbance. A few cases are associated with pronounced evidences of nervous excitation, such as restlessness and delirium, while others, on the other hand, simulate the effects of a narcotic, sleep and coma being the prominent features.

The minimum fatal dose of arsenic is generally stated as $1\frac{1}{2}$ or 2 grains (0.09 to 0.13 Gm.). Reese considers, however, that such an assertion rests on insufficient evidence, and believes that 10 grains (0.65 Gm.) comprise the amount that will prove fatal in most untreated cases.

Much larger amounts than those mentioned above have been recovered from, a large part of the drug ingested having probably failed to enter the system owing to vomiting induced by it. It is well to bear in mind, however, that idiosyncrasy may cause even minute doses to prove toxic, and that it is advisable always to begin with small doses.

Katchkatchev has reported an instance of remarkable idiosyncrasy toward arsenic in a student suffering from malaria who had begun to take Fowler's solution, beginning with 2 drops (0.12 c.c.) at a dose. Three hours after the first dose he presented all the classical symptoms of acute arsenic poisoning; nausea, vomiting, diarrhea, tenesmus, enteralgia, spasmodic cough, and paresis of the extremities. All these disturbances passed away by the following morning. Not suspecting the true source of trouble, the patient took another dose of 3 drops (0.18 c.c.) of Fowler's solution, and shortly after the same train of symptoms again set in, with such violence that antidotal measures had to be employed.

Two patients treated with sodium cacodylate showing acute symptoms following injections. The hypersusceptibility to the drug resulted in extensive local inflammatory swelling, marked rise in temperature, general malaise, headache, diffuse pains in the joints, loss of appetite, and, in one case, dyspnea. C. Staeubli (Deut. med. Woch., Dec. 26, 1912).

In a case of supersensitiveness to arsenic after from 2 to 4 injections of cacodyl had caused no reaction whatever, the author observed after every subsequent injection a large and firm local infiltration about the size of a silver dollar, which felt warm and itched violently, though not painful. It underwent involution with desquamation in the course of a few days. The phenomenon suggested in every way not simple irritation but anaphylaxis. Kaufman (Deut. med. Woch., Feb. 6, 1913).

Two cases of oversensitiveness to organic arsenic preparations (arsenophenylglycin and salvarsan) in which there appeared an extensive exanthem while examination of the blood revealed a marked eosinophilia. Schlecht (Münch. med. Woch., Apr. 15, 1913).

The usual period of survival in fatal cases ranges from about ten to forty-eight hours. Taylor, cited by Reese, reported the case of a youth who suc-

cumbed in twenty minutes, after showing symptoms of a tetanic character. This is, however, the shortest period on record. Frequently the patient lives over twenty-four hours after ingesting the fatal dose. In some cases, in which the amount absorbed has not been sufficient to cause early death, life is prolonged for from two days to a week, or even longer. In these patients, a diminution in the vomiting, purging, and pain may take place at the end of twenty-four or forty-eight hours; circulatory embarrassment, thirst, and albuminuria continue, however, and in a short time edema, cyanosis, cramps, and convulsive phenomena make their appearance, followed by coma and death. A skin eruption sometimes appears in these delayed forms of arsenic poisoning.

Report of 2 typical cases of industrial poisoning with arseniureted hydrogen. One patient had had two similar but milder attacks one and three years before. In both cases there was an olive-green tint of the skin, probably the result of the combination of anemia and jaundice. Both patients were taken suddenly with headache, chilliness, vomiting, fever, hemoglobinuria, appearance of large amounts of bile in the stool, slight enlargement and tenderness of the liver, and enlargement of the spleen. The symptoms came on after working for a few hours plating lamps with a mixture containing hydrochloric acid, zinc, and arsenic. The patients lay in a state of stupor for a week; then one rapidly recovered. The other displayed more of a hemorrhagic diathesis, and intercurrent typhoid the third week brought him to death's door, but he finally recovered, although convalescence was delayed by a hemorrhagic nephritis. A special feature of the blood picture was the large numbers of erythroblasts, up to 3544 per c.mm. in the first and 43,377 in the second

case. Joachim (Deut. Archiv f. klin. Med., c, Nu. 1 and 2, 1910).

In cases which do not end fatally, disturbances of digestion, sensation, and motion are apt to delay the final recovery. The sensory phenomena witnessed include anesthesia, hyperesthesia, pain, etc. Motor paralysis may lead to early atrophy of muscles, but in these cases there is a marked tendency to subsequent recovery of function. Of 100 cases of arsenical paralysis studied by Imbert-Gourbeyre all but 3 recovered according to Horatio C. Wood, Sr.

Arsenical paralysis giving the same symptoms in 3 members of the same family. Arsenic was contained in some flour which all the patients had eaten. All 3 were seized with symptoms of acute arsenic poisoning, and within a fortnight developed the same symptoms of arsenical paralysis. They were troubled with anesthesia and paresthesias in the extremities, inability to work and to walk. The gait was unsteady and they were unable to stand with feet close together. Their walk was slow, rigid, and irregular. There was left facial paresis and abolition of the tendon reflexes, but no affection of the sensory nerves and no paresis of the upper extremities, save that in 1 of the 3 patients there was slight paresis of the fingers and thumb. The peculiar feature of these cases was that the paralysis was identical in all 3 instances, possibly owing to hereditary peculiarities. Luigi Ferrannini (Riforma medica, June 3, 1903).

Case of a man of 39 who had presented for 3 months symptoms of pseudotabes from arsenical peripheral polyneuritis. The condition is ascribed by the writer to poisoning from arsenic with which the drinking water in the Bell Ville region, Argentina, is known to be impregnated. Zayas (Semana Medica, Buenos Aires, Jan. 10, 1918).

DIAGNOSIS OF ACUTE ARSENIC POISONING.—The most characteristic and prominent symptom being a watery diarrhea, the chief conditions to be excluded are cholera nostras and cholera Asiatica. In the absence of a history of taking the poison, diagnosis may be extremely difficult. The Asiatic form of cholera, however, may be practically ruled out where no epidemic of the disease is known to be present. In cholera morbus the diarrhea is less likely to be associated with the passage of shreds of mucous membrane and blood than in arsenic poisoning, and the pain in this form is also generally less marked. Chemical tests upon the excreta may, nevertheless, in a few cases be the only means of differentiation.

From poisoning by strong acids or alkalies, arsenic poisoning is distinguished by the absence of corrosion of the mouth and throat, while from poisoning by metals such as mercury and lead the greater rapidity of onset will afford differential evidence.

Of the *pathological changes found post mortem*, evidences of gastroenteritis are the most prominent. The gastric mucosa is markedly reddened, either diffusely or in patches. It is often abnormally soft and may be covered with a sticky magma consisting of exuded mucus mixed with arsenic. Ulceration, however, is rarely present. Various parts of the intestine may show lesions corresponding to those present in the stomach; most frequently the upper portion of the small intestine, the cecum, and the rectum are involved. The gut may be found filled with watery fluid containing loose shreds

of mucous membrane. Upon microscopic examination the epithelial cells of the intestinal mucosa show pronounced granular or fatty changes. It must be noted, however, that in occasional instances all evidences of irritation of the gastrointestinal tract are unaccountably wanting (Reese).

Other organs, such as the liver, kidneys, and even the muscles, may show alterations of their parenchyma analogous to those found in the alimentary tract. More frequently, however, hyperemia is alone present. Changes in the central nervous system may in some instances be detected. Thus Erlicki and Rybalkin, according to Wood, found myelitis in a case of arsenic poisoning. Popoff, experimenting upon dogs, likewise noted myelitis, and, in cases where the period preceding death was longer than usual, observed granular changes in the protoplasm, shrinkage of the nuclei, and vacuolization, in the cells of the spinal gray matter. Alexander, on the other hand, found atrophy of peripheral nerves and changes in the muscle tissue of rabbits poisoned with arsenic (Wood).

The authors tested the action of arsenical compounds on the adrenals on male guinea-pigs and also on rabbits and dogs by intravenous administration.

The compounds tested comprised arsenous and arsenic acids, sodium cacodylate, atoxyl, arsacetin, arsenophenylglycin, salvarsan, and neosalvarsan. Sterile solutions of the substances were injected intraperitoneally in black and in white animals respectively. The writers conclude as follows: (1) Toxic doses of all arsenicals produce definite pathological changes in the adrenals of guinea-pigs. These include congestion, hemorrhage, disturbances in the lipid content, cellular degenerations

and necroses, and reduction in the chromaffin content. (2) The character and severity of the injury produced by different arsenicals varies with the chemical constitution of the compounds. (3) From these facts they believe that adrenal injury is an important factor in arsenical intoxication. Brown and Pearce (Jour. of Exper. Med., Nov. 1, 1915).

As a rule, the cadavers of victims of arsenic poisoning remain well preserved for a long period after death, owing to the inhibitory effect of the drug on putrefactive bacteria. In a few instances, however, decomposition has been known to progress as usual notwithstanding the presence of arsenic.

TREATMENT OF ACUTE ARSENIC POISONING.—The first consideration is to secure a quite thorough evacuation of the stomach by washing it out repeatedly with the aid of a stomach tube or giving an emetic. There is official in the U. S. Pharmacopeia a chemical antidote for arsenic,—*ferri hydroxidum cum magnesiæ oxido*,—which is made as follows: Mix 10 drams (40 c.c.) of liquor ferri tersulphatis with 4 ounces (125 c.c.) of water. Rub $2\frac{1}{2}$ drams (10 grams) of magnesium oxide with cold water to a smooth, thin mixture, transfer to a one-liter bottle, fill the latter three-fourths full with water, and shake. Add the magnesia mixture gradually to the ferric sulphate solution in another bottle and shake. There is thus formed a precipitate of ferric hydroxide, which is believed to enter into a loose chemical combination with the arsenic, thus fixing it and tending to impede its toxic action. It is necessary that the preparation be fresh, and that it be given in large amounts, *e.g.*, in rapidly repeated

tablespoonful doses until 4 ounces (125 c.c.) have been administered, after which its evacuation from the stomach with the combined arsenic should be secured, and a **saline** or **castor-oil purge** then given. Where the official antidote or its ingredients are not quickly obtainable, other solutions of iron salts, such as the **tincture of ferric chloride**, **Monsel's solution**, etc., together with **magnesium carbonate**, **sodium carbonate**, or any alkali, may be used. The precipitate of iron hydrate should preferably, under these circumstances, be placed on a piece of muslin and washed with water before it is administered. **Dialyzed iron**, freshly precipitated with a small amount of alkali, or freshly **calcined** or **precipitated magnesia** alone, can be used as inferior substitutes for the official antidote in an emergency (Wood). It should be stated that the implicit confidence hitherto placed in **ferric hydroxide** as an antidote has recently been somewhat shaken through experiments performed by De Buscher, which have tended to show that the combination formed by it with arsenic is more soluble than the trioxide of arsenic itself, and hence offers no assurance of non-absorption of the poison. Nevertheless, at least a certain degree of usefulness on the part of the iron precipitate seems to have been established through practical experience.

The author was able to save animals to which a lethal dose of Fowler's solution had been given by mouth or subcutaneously, by injecting full doses of **magnesium sulphate** hypodermically. Animals poisoned intravenously, however, could not thus be saved. The magnesium acts, therefore, only before the arsenic

has entered the blood and combined with the tissue cells. Its effect is probably produced through retardation of the absorption of the arsenic owing to the formation of magnesium arsenic compounds that are only slightly soluble. D. Sieber (Arch. Internat. de Pharm. et de Therap., vol. xxii, Nos. 3 and 4, 1913).

The remaining measures to be taken in the treatment of acute arsenic poisoning include the administration of **opium** to check vomiting and diarrhea, **saline hypodermoclysis** to make up for the fluid already lost and stimulate the renal eliminatory function, **demulcent drinks** to soothe the inflamed mucous membranes, and various stimulating remedies, such as **digitalis**, **strychnine**, **caffeine**, **camphor**, etc., together with **external heat**, in cases which have advanced to the stage of collapse.

CHRONIC ARSENIC POISONING.—Symptoms of chronic arsenic poisoning may result either from the continued medicinal use of excessive doses of the drug or from its prolonged absorption through the lungs, skin, or alimentary tract by those whose work, food, or surroundings bring them more or less constantly under its influence. Workers in aniline dyes or copper occasionally show it. Wall-papers colored with arsenic formerly were responsible for many cases; the poison escaped into the atmosphere as a fine dust or vapor, but this danger has of late practically disappeared owing to preventive legislation.

Epidemics of arsenic poisoning have occurred in England due to contaminated glucose used in the manufacture of beer. In Halifax an epidemic of arsenic poisoning was caused by the

use of malt which had been prepared with coke impregnated with arsenic.

According to Haywood and Warner, fixed compounds of arsenic in wall paper or fabrics may be so changed by the growth of molds that the arsenic is free and discharged in the atmosphere of rooms. In this way the inhabitants of rooms become the subjects of intoxication, usually manifested by supraorbital neuralgia, pain in the eyes, vague pains in the fronto-nasal region and in other parts of the body, restlessness at night, depression during the day, gastrointestinal disturbances, and slight fever. The most important symptoms are the orbital neuralgia and the lassitude. In rare cases skin eruptions, suppuration of the fingers, discharge from the ears, inflammation and ulceration of the ear passages, and other symptoms, have been observed.

Certain cosmetics containing arsenic, clothing fabrics and furs treated with it, as well as stuffed animals, have also given trouble. An epidemic of chronic arsenic poisoning occurred in England from the use of a beer in the preparation of which sulphuric acid containing arsenic as an impurity had been used.

A considerable degree of tolerance to arsenic may be acquired by continued oral use of gradually increasing doses. Thus, the so-called "arsenic eaters" among the peasants of Styria, in southern Austria, are said to be able to take doses of 8 grains (0.51 Gm.) of arsenic with impunity. It has been practically proven, however, by experiments in animals, that the supposed systemic tolerance is not present, but is merely simulated by a diminished power of absorption of the drug from the alimentary tract. Hypodermic injection of relatively small amounts of arsenic in animals habituated to it *per oram* caused death, as though no true general tolerance

had been acquired. It thus seems quite possible that where arsenic enters the system by being inhaled or absorbed through the skin, no pronounced degree of tolerance will be developed.

Besredka found that when a large non-lethal dose of arsenic is given to guinea-pigs, the leucocytes in the peritoneal fluid diminish greatly in number, the larger the dose the greater being the diminution. This lasts for ten or twelve hours, and is succeeded by great hyperleucocytosis. The animal is ill and out of sorts during this time, but in two or three days the blood becomes normal again, and vivacity and appetite are recovered. In the peritoneal exudation the phagocytic leucocytes take up the arsenic in small granules; the lymphocytes do not do so. During the diminution it is the former which disappear, while the latter persist. Phagocytic protection is also probable. EDITORS.

Starting with $\frac{1}{100}$ -grain (0.001 Gm.) doses of arsenious oxide after meals, the writer gradually reached the dose of $1\frac{1}{2}$ grains (0.078 Gm.), which produced irritability and distinct and lasting discomfort every way it was taken and all precautions notwithstanding. In 1-grain (0.065 Gm.) doses the drug could only be taken with comfort if dry foodstuffs were consumed at meals; if liquid beverages or soft foods were partaken of, the administration of the grain (0.065 Gm.) dose of As_2O_3 produced immediate discomfort and burning pains in the abdomen, lasting 40 minutes to 1 hour followed by diarrhea. Harding (Lancet, Jan. 24, 1914).

The volatilization of solid arsenic in the human body, the cause of which is the "garlic breath" in arsenic eaters, probably takes place in the intestine as the result of the activities of certain bacteria, experiments having duplicated this behavior *in vitro*. A number of organisms seem to possess the power of transforming the arsenic into a gaseous form. Puntoni (Gaceta Med. Catalana; Med. Rec., Feb. 3, 1917).

The earlier symptoms of chronic arsenic poisoning vary somewhat according to the mode of introduction of the drug. Where it has been administered by mouth for therapeutic purposes, the first sign of poisoning is frequently a swollen condition of the eyelids, and puffiness below the eyes, which may be closely followed by congestion of the conjunctivæ and dryness, later increased secretory activity, of the nasal and pharyngeal membranes. Where the poison has been taken into the system by inhalation, frequently signs of bronchial irritation may be the first to appear. Another typical and early manifestation of chronic arsenic poisoning is disturbance of the gastrointestinal functions. The subject loses his appetite, complains of nausea, sometimes of vomiting and of pain in the stomach region, and of diarrhea.

Skin eruptions also occur very frequently; they may be of various types—erythematous, urticarial, papular, pustular, etc. More characteristic than these, however, are the modifications which take place in the superficial layers of the skin in long-standing cases. These consist chiefly of an overgrowth of the horny layer, especially on the palms and soles. There is at first, according to Jamieson, hyperidrosis of these areas, followed by the formation of warty corns around the orifices of the sweat-glands, and later a diffuse hyperkeratosis, associated with burning sensations. Finally, there results an exfoliation of scales from the epidermis. In prolonged cases of poisoning, loss of hair and of finger-nails may occur. In a few cases the liver is found enlarged; jaundice may be

present. More frequently witnessed, however, is a peculiar dark pigmentation of the skin—arsenic melanosis. Hutchinson reported a case in which, in addition, there were numerous large, black freckles on the face, while Foerster recorded that of a boy of 10 years who, upon taking 1 ounce of the liquor potassii arsenitis of the German Pharmacopeia in the course of two months, developed exophthalmos, thyroid pulsation, and a yellowish discoloration of the skin, face, and trunk, which gradually deepened into brown.

J. C. Muir has found that the blood of arsenical patients having deep cutaneous pigmentation is decidedly richer in red cells and hemoglobin than that of similar slightly pigmented or unpigmented cases. This, he maintains, disproves the almost universally accepted hypothesis that the pigmentation is due to destruction of hemoglobin or red cells, and is evidence for thinking that the melanin of the skin is an important element in the production of hemoglobin. The erythroblastic function of the marrow is more easily stimulated in the presence of a large store of cutaneous melanin.

Case of a woman suffering from facial acne who was ordered liquor arsenicalis. In three weeks the acne had disappeared, but the face and body became pigmented with a yellowish color. The color afterward resembled that of Addison's disease. It disappeared after the drug was stopped. In another patient with acne, who was taking liquor arsenicalis, herpes facialis and cervicalis occurred after three weeks. A fresh attack occurred when arsenic was resumed. This case is interesting, considering that arsenic is the drug usually prescribed for herpes zoster. Stark (*Presse médicale*, No. 81, 1901).

Report of 4 cases of keratosis following the long-continued administration of arsenic, in 1 of which

epithelioma of the finger supervened. The keratosis was of the circumscribed variety and affected the palms and soles, appearing as small, corn-like elevations. In 3 of the 4 cases it had been taken for psoriasis, in the one in which the epithelioma occurred for twenty years almost continuously. The microscopic changes consisted of circumscribed thickenings of the corneous layer, atrophy of the derma, and complex alterations in the papillary layer. In no instance did he find any relation between the epidemic alterations and the sweat-ducts.

The sequence of cancer is very exceptional, only 19 cases being on record, usually beginning many years after the initial keratosis had shown itself, and sometimes when the drug had been stopped for many years previously. When epitheliomatous changes have taken place the course of the case is frequently rapidly malignant. Dubreuilh (*Annales de dermat. et de syphil.*, No. 3, 1910).

Anemia is a common result of prolonged use of large amounts of arsenic.

Another important accompaniment of chronic arsenic poisoning is neuritis. This may occur also as a sequel to acute poisoning where the amount of arsenic absorbed is insufficient to cause death. It is more usually seen, however, in the chronic type of poisoning, and is delayed until the drug has had opportunity to accumulate in the system for three or more weeks. The neuritis is typically multiple, and generally involves the limbs rather than the trunk. The earliest manifestation is often a sharp pain at one or more joints, together with headache, followed by disturbances of sensation such as hyperesthesia, itching, diminution or exaggeration of temperature sense, etc. The condition "erythromelalgia"—swell-

ing, redness, and extreme sensitiveness to touch of the skin of a part—may appear.

Case of arsenic neuritis in a girl of 23, who was treated for chlorosis and palpitation by arsenic in increasing doses. Commencing with a single drop (0.06 c.c.) twice daily, the dose was increased each day a drop (0.06 c.c.) until 10 drops (0.6 c.c.) were taken twice daily. This dose was then taken for six weeks. When 15 drops (0.9 c.c.) daily were being taken, the first symptoms of intoxication appeared in the shape of edema of the feet, hands, and face. As the doctor persisted in the use of arsenic, pigmentation set in. There was frequent micturition, pain and burning in the urethra, and hematuria. Later there was neuritis, involving the legs first and then the arms, with paresthesia and paresis. The patient continued the arsenic till she was quite bedridden, when she was removed to a hospital. The condition gradually improved during a stay in the hospital of three months, and ultimately a complete cure was obtained. (*Wiener klin. Rundschau*, Nu. 41, 1901).

Next comes paralysis of sensation, followed, in turn, by motor paralysis. The affection is usually symmetrical, and shows a predilection for the extensor muscles of the foot and the peronei in the lower limb, while in the upper extremity the extensor muscles in the forearm are chiefly involved. If the cause persists, atrophy of the muscles takes place, producing foot-drop and wrist-drop. Herpes zoster may be an accompaniment of the nervous involvement.

Case of a young girl aged 16, of good family history, suffering from anemia, for which she had been treated in the ordinary way without much success. Hypodermic injections of citrate of iron, arsenate of soda (1 mg.— $\frac{1}{100}$ grain), and strychn-

nine were therefore given (33 injections in all). About the eighteenth or twentieth day the patient began to complain of severe pains in the lower limbs, tingling pains in the toe and sole of the foot, difficulty in standing or walking, and some hyperesthesia; about a week later these sensations were more exaggerated, with girdle pains, transitory incontinence of urine, headache, and some amyotrophy. There was no rash. Similar symptoms came on in the upper limbs. Later, the kneejerks were lost and a certain amount of inco-ordination was observed. Reaction of degeneration was found in the extensors of the foot and a quantitative modification in some of the muscles of the leg, thigh, and forearm. All these symptoms were more marked on the right side. On cessation of the treatment, **massage** and **galvanism** cured the patient in a month and a half. Donetti (*Riforma medica*, Jan. 24, 1900).

The writers call attention to disappearance of the Achilles tendon reflexes as an early sign of chronic arsenical poisoning in paretics subjected to intensive neoarsenobenzol treatment in the daily intravenous dose of 0.3 Gm. (5 grains), up to an aggregate dose of 12 Gm. (3 to 5 drams). The loss of the reflex indicates a latent arsenical neuritis of the internal popliteal nerve, unaccompanied by disturbances of locomotion, pain or muscular atrophy, yet already resulting in certain quantitative modifications of the electric reactions in the involved muscles. Paretics subjected to such treatment show marked physical and mental improvement, but there is no clinical or humoral cure, the Bordet-Wassermann reaction in the cerebrospinal fluid persisting. Sicard and Roger (*Paris méd.*, June 29, 1918).

The final stage of chronic arsenic poisoning is characterized by mental apathy, anemia, emaciation, loss of the hair, salivation, and a tendency to

hemorrhagic extravasations. Fatty degeneration in various viscera takes place, and death may occur from exhaustion.

DIAGNOSIS OF CHRONIC ARSENIC POISONING.—This may be a matter of some difficulty, owing to the variety of the symptoms, and especially to the fact that the physician is apt to overlook the possibility of chronic arsenic intoxication because of its rarity. In the event of a history of taking the drug the diagnosis is of course plain. If such a history be not obtainable, however, a positive diagnosis will rest upon the chemical detection of arsenic in the urine.

Clinically, the conditions most readily confused with chronic arsenicalism are lead poisoning and alcoholic neuritis. Lead paralysis is to be distinguished from that of arsenical neuritis by the blue line on the gums, the greater incidence in the upper limbs, the lack of involvement of the supinator longus and flexor muscles, and the constipation. Paralysis of alcoholic causation may be differentiated by the characteristic facial appearance of the patient, the mental condition, and the history of excessive indulgence in alcoholics. *Tabes dorsalis* may be in certain respects simulated by chronic arsenic poisoning, but seldom closely enough to deceive.

Hyperesthesia of the skin and muscles, while not always absent in alcoholic neuritis, is much more consistent and generally severe in cases due to arsenic. The vasomotor phenomena are also very striking in the arsenical cases and very rarely present in the alcoholic. In one epidemic, ataxia was frequently noted in the arsenical cases,

while comparatively infrequent in the alcoholic. (Bury.) * *

The most convenient tests for arsenic in the urine are the following:—

1. *Reinsch's Test*.—This is made by adding to the urine, preferably already concentrated by boiling, $\frac{1}{4}$ of its volume of hydrochloric acid and a bit of shining copper-foil. The mixture is boiled for some minutes, when, if arsenic be present, the copper will be observed to tarnish and darken in color to gray or black.

2. *Gudseit's Test*.—In a test-tube place a little metallic zinc, a few cubic centimeters of dilute hydrochloric acid, and a few drops of iodine solution; then add a few cubic centimeters of the urine. Promptly place over the orifice of the tube a cap of filter paper which has been moistened with a saturated solution of silver nitrate. In the presence of arsenic, a lemon-yellow color will appear on the filter paper, which will then turn black if a drop of water be placed on it. It is necessary, in performing this test, first to make sure that the reagents used do not contain arsenic; this may be done by placing the filter paper for a few minutes over the mouth of the tube before the urine has been introduced (Todd).

TREATMENT OF CHRONIC ARSENIC POISONING.—In addition to the removal of the patient from further contact with the drug, elimination of the arsenic already present in the system should be hastened by means of **potassium iodide**, **saline enteroclysis**, and **purgation**. The disturbances in the gastrointestinal tract should be treated with **bismuth**, **demulcents**, and other like sedatives. Plenty of good food should

be given to counteract the emaciation likely to be present. Arsenical neuritis, if it exists, may require **analgesics** at first; later, **massage** and **electric treatment** will be indicated to re-establish the function of the affected nerves and prevent muscular atrophy.

According to Bury, **warm fomentations** are useful in relieving the pain and **sodium salicylate** and **potassium iodide** are also of some service. **Strychnine** should not be given early in the affection.

THERAPEUTICS. — Internal Uses.—In certain anemias arsenic in moderate doses increases the number of erythrocytes, and is therefore especially useful in **progressive pernicious anemia** and in secondary anemias where the red-cell count is low. Unfortunately, its beneficial effect is generally not of long duration, a relapse usually taking place at a time when the prospects of recovery seem brightest. In **chlorosis** arsenic is ineffective when given alone, but assists the action of iron if administered in combination with it. In the several forms of **leukemia** and in **pseudoleukemia** arsenic is one of our most useful remedies, tending in many cases both to diminish the number of white cells and increase the erythrocytes; on the whole, however, the results are even less to be depended upon than in the progressive pernicious type of anemia. The most convenient method of prescribing arsenic in these cases is to give Fowler's solution internally, beginning with doses of 2 minims (0.12 c.c.) after each meal and increasing by 1 minim (0.06 c.c.) every day, provided no untoward effects appear, until 15 or 20 minims (0.9 to 1.2 c.c.) are being

taken. The medication should be intermitted for a week at rather frequent intervals in order to avoid excessive storage of the drug in the viscera.

In various **cachectic conditions** arsenic not only tends to improve the condition of the blood, but exerts a very favorable effect upon the general nutritive state by virtue of its so-called "alterative" action. Thus, in the cachexia of **chronic malaria**, especially in cases where the specific effect of quinine has worn off, arsenic in the form of ascending doses of Fowler's solution or the trioxide is a remedy of acknowledged worth. In the neuralgic paroxysms of masked intermittent fever, arsenic is also often of great value. Its effect may oftentimes be enhanced by combination with iron and quinine. As a rule, full doses of arsenic are required in malaria. Where, after a time, the stomach rebels under it, the hypodermic method of administration should be resorted to. According to Downie arsenic is valuable as a prophylactic against malaria. Some authors counsel the administration of arsenic and iron in ordinary cases of intermittent fever, after the paroxysms have been subdued with quinine.

The progress of malignant tumors such as **epithelioma** and **sarcoma** is sometimes retarded by the internal administration of arsenic. Koenigsberg reported a case of sarcoma of the head of the tibia which he claimed had recovered through the influence of this remedy. It is well known, too, that various forms of **verruca**, including the common wart, are sometimes caused rapidly to disappear by arsenic, given in conjunction with external treatment; the use of the drug is especially advantageous where multiple lesions are present.

Müller recommends for children Fowler's solution in the commencing dose of $\frac{1}{4}$ minim three times a day gradually increased.

In the various painful neuroses included under the name **gastralgia**, Sawyer strongly recommends the trial of arsenic trioxide in $\frac{1}{24}$ -grain (0.0027 Gm.) doses, given in a pill with 2 or 3 grains (0.13 to 0.2 Gm.) of extract of gentian three times daily, midway between meals. In cases of moderate severity, according to this author, no other treatment is needed, though in more pronounced cases, counterirritation to the epigastrium should be used in addition. A varied dietary should at the same time be prescribed, and the arsenic continued for some weeks.

In **diabetes mellitus** arsenic is frequently of service. Forchheimer prefers it to opium in this affection and recommends that it be given in the form of Fowler's solution in ascending doses until mild toxic effects are produced, when the dose should be gradually diminished. It is especially indicated in the severe cases, in combination with the usual dietetic treatment, and is very valuable in neurotic, debilitated subjects. Forchheimer found that repeated courses of arsenic did not lose their effect in diminishing the glycosuria and the production of acetone bodies.

In **bronchial asthma** arsenic is not infrequently a useful remedy for continuous administration in the intervals between paroxysms. The best results according to Musser are obtained in the young. Arsenic may also with advantage be added in the cigarettes of stramonium and hyoscyamus leaves often used in this affection. Prevailing views as to the action of arsenic offer no definite clue as to the manner in

which the drug exerts its effects in asthma.

The same is true of the use of arsenic in the **vomiting of pregnancy**, as recommended by Aulde, who prescribes it in the following combination:—

R. Arseni trioxidi,
Ext. ignatie,
 of each gr. ss (0.03 Gm.).
Pulv. ipecacuanhæ,
Ext. cascariæ sag-
radæ.....of each gr. xv (1.00 Gm.).
Olei gaultheriæ, .. m ij (0.12 c.c.).

M. et ft. in pil. no. xx.

Sig.: One pill after meals.

The patient should be advised to restrict the use of fluids at meals, and drink principally between meal hours.

The favorable influence of arsenic upon nutrition also renders it useful in **pulmonary tuberculosis**. Bonney finds that through its employment a marked improvement in the appetite sometimes occurs. He advises the use of 1 minim (0.06 c.c.) of Fowler's solution three times daily as an initial dose, cautiously increased to 5 minims (0.3 c.c.). The preparation should be given in a half-glassful of water after meals, and may, if desired, be combined with strychnine. After two months its administration should, as a rule, be stopped, at least for a time. Arsenic has been credited by some with the power of arresting night-sweats in phthisis.

In **rickets** small doses of arsenic have sometimes proven of great value.

In **arthritis deformans** arsenic is among the drugs which, if given early in the disease, do the most good. It may with advantage be alternated with iron, and should be administered for some months after the preliminary acute manifestations have disappeared.

In the treatment of certain **nervous**

conditions, especially **chorea** and **neuralgias**, arsenic has a well-deserved reputation. In the former affection it should be given in rapidly ascending doses until, in a child 10 years old, *e.g.*, 35 minims (2.1 c.c.) of Fowler's solution are being taken daily, or vomiting appears. If no untoward effect shows itself, the amount given should be gradually decreased. In chronic choreic cases large doses often prove very effective where smaller ones have already been found useless. The drug should be given after food, and the little patient required to lie down for a half-hour afterward in order to avoid nausea and vomiting.

The writer's experience sustains the view that minute, long-continued doses of arsenic exert a stimulating action on nerve tissue. The benefit was marked in 8 out of 12 cases of **multiple sclerosis** in his experience. The improvement was at first mostly subjective, the patients gaining in weight and feeling better generally, and this was soon followed by better functioning of the legs, some patients even being able to take long walks, when before they could not even stand without assistance. The best results were obtained in cases of uncomplicated multiple sclerosis in which the optic nerve was still intact. H. Willige (Münch. med. Woch., Mar. 22, 1910).

In many **chronic skin diseases** arsenic is a most valuable remedy, though in acute cutaneous conditions it is, on the contrary, harmful. It is conceded to improve in some way the nutrition of the superficial layers of the skin. **Psoriasis** is in many instances considerably benefited by Fowler's solution, given in doses of 3 to 5 minims (0.18 to 0.3 c.c.) in water after meals, slowly increased until the maximum of benefit is obtained or the limit of tolerance is

reached. According to Stelwagon, the official solution of sodium arsenate is better borne in patients with sensitive digestive tracts than Fowler's solution, and should therefore be given the preference over it. This author also suggests that in robust, plethoric patients exhibiting lesions of distinctly inflammatory aspect, liquor potassii hydroxidi, in doses of 10 to 30 minims (0.6 to 1.8 c.c.), be given in combination with the arsenic preparation. It has been recommended to begin the arsenic treatment in psoriasis with a saline diuretic such as potassium acetate or bitartrate. In rebellious cases of the disease, or where prompt effects are particularly desired, hypodermic injections of Fowler's solution or of sodium cacodylate may be given. Herxheimer gave intravenous injections of arsenic trioxide in 25 cases of psoriasis, in doses ascending from $\frac{1}{60}$ grain (0.001 Gm.) to $\frac{1}{4}$ grain (0.016 Gm.); 10 cases were completely cured, 6 much relieved, and 9 reported as still under treatment, but greatly improved.

In some cases of **chronic eczema**, where moisture is absent from the lesions, and the latter are chiefly papular and scaly, arsenic is to be remembered as of possible benefit; it is not by any means so dependable, however, as in psoriasis, and in some cases in which it is tried may have to be given up because of aggravation of the disease.

In **acne** of the slowly evolving papular type, especially where anemia is present in addition, arsenic often proves effective, though the digestion may be disturbed by it if it is not cautiously used. In more acute types of acne it is likely to do more harm than good.

Other skin diseases in which arsenic has proven of special value are **pemphigus** (in which it should be given for

a prolonged period in gradually increasing doses), **lichen planus**, **dermatitis herpetiformis**, and **alopecia areata**. It may also, though less frequently, prove beneficial in resistant cases of **seborrhea** and **chronic urticaria**.

It may be generally stated that arsenic is a drug of undoubted value in a limited number of skin diseases, especially in **psoriasis**, **lichen planus**, and **acute pemphigus**. It is useful in the quiescent stages of the first two diseases when the active inflammatory symptoms have subsided. Even when used in appropriate cases and at the proper stage, it often fails lamentably.

Arsenic is excessively and indiscriminately prescribed by practitioners in the treatment of skin diseases. It is a potent drug exercising a stimulating and later on irritative influence upon nerve structure. When used in too large doses or over protracted periods, it may produce profound structural changes in the nerves. Sensory, motor, and trophic disturbances of a serious character have resulted from its injudicious use.

The noxious influence of arsenic is often exerted upon the skin. Not only are inflammatory dermatoses commonly aggravated by its use, but a great variety of skin manifestations may be produced by toxic doses. The drug should not be administered unless there is a good reason for its use, and, above all, patients must be instructed not to continue the remedy upon their own judgment, as is so commonly done. Physicians should not permit prescriptions for arsenic to be renewed without their specific sanction. Jay F. Schamberg (*Therapeutic Gazette*, June 15, 1908).

[The production of cancer through the injudicious use of arsenic recalls a series of cases of arsenical cancer described by Mr. Jonathan Hutchinson many years ago: 1. A man, aged 35, had keratosis of the palms and had three growths excised from different parts in 7 years. 2. A man, aged 46, was emaciated and very ill. Cancer developed in an old psoriasis patch

on the abdomen and also on the back. His hands became harsh and dry, but corns did not form. He had taken arsenic since the age of 14. 3. A lady had taken arsenic for long periods for lupus. In December, 1888, her palms and soles were in a condition of keratosis and arsenic was forbidden. In July, 1890, the palms and soles had recovered. At one time in 1877, while taking arsenic, the edge of the lupus patch assumed the hard-rolled condition of rodent ulcer. 4. A lady, aged 45, who for a long time had keratosis of the palms, had a squamous-celled epithelioma of the neck as big as a child's fist. Thickened, ulcerated skin had twice been excised from her palms. The interval between the date of suspension of arsenic and the development of keratosis may be prolonged over many years. In 1 typical case of arsenical cancer the arsenic was taken in early life and the cancer did not develop until senility. Ed.]

In the treatment of **psoriasis**, arsenic seems to do best in recent cases and such as have not had other arsenical treatment. In **lichen planus** it is generally admitted to be a useful remedy. It is most effective when the eruption occurs in limited areas and when there is little or no itching. If the greater part of the skin is involved and there is marked pruritus, it is apt to aggravate the latter and seems to influence the course of the disease but little. In such cases other remedies, such as the salicylates, will be found more useful. In **pemphigus**, while hardly a specific or even curative, it is one of the most useful internal remedies, diminishing the liability to relapse and lengthening the intervals between the outbreaks. Much the same can be said as regards its value in **dermatitis herpetiformis**.

There is considerable evidence that arsenic, especially when given hypodermically, is sometimes useful in **sarcoma** of the skin, and more particularly in the form described by Kaposi as "idiopathic multiple hemorrhagic sarcoma." The writer has seen an apparent arrest of the disease under its influence. In a small

number of cases arsenical treatment has appeared to be useful in **mycosis fungoides**, but, in the opinion of most authors, little is to be expected from it in the majority of cases. M. B. Hartzell (Jour. Amer. Med. Assoc., Oct. 31, 1908).

It is in the patients who have suffered from psoriasis that epitheliomatous developments due to arsenic have most frequently been recorded. Some 30 cases are now on record. The writer describes a case of his own in a woman. In spite of operative removal, death occurred, apparently from internal metastatic growths, about 2 years after the first came under medical treatment. R. Pye-Smith (Lancet, July 19, 1913).

From 1885 to 1912 only 15 cases of arsenical cancer have been reported out of hundreds who have been taking arsenic for long periods without getting cancer. The total number of cases is insignificant and negligible compared with the number of those taking arsenic for various diseases, habitual eaters, and the total incidence of cancer. The right clue is to be found in the local applications. The occurrence of cancer 10, 20, or 30 years after discontinuing the internal use of arsenic is due to abnormal cell proliferation induced by the external application of chrysarobin, pyrogallol, tar, and other chemical irritants to patches of psoriasis for several years, before, during, and after the internal use of arsenic. The same is true in cancer occurring upon lupus vulgaris, lupus erythematosus, and syphilis. Keratoses and warts, whether due to arsenic or to other causes, have a tendency to undergo cancerous degenerations when subject to chronic irritation and injury, but there is no special liability where arsenic has been given internally for a long time. Arsenic is only responsible for the production of the keratotic condition, or preparation of the favorable soil, but the development of cancer is quite independent of arsenic. C. E. de Silva (Med. Press, Mar. 27, 1918).

In certain constitutional diseases, due to animal parasites, other than malaria, which has already been mentioned, arsenic has an important field of use. In **trypanosomiasis** it has been found particularly effective, and is administered chiefly in the form of atoxyl (*q.v.*). For information concerning the arsenic preparations lately brought into use in **syphilis**, the reader is referred to the headings Dioxydiamido-arsenobenzol, Cacodylic acid, etc. Donovan's solution (liquor arseni et hydrargyri iodidi) has been extensively employed in the anemia of syphilis, and combines the beneficial influences of the 3 remedies which are of greatest value in this affection.

In cases of **syphilis** which no longer respond to mercury, the writer has used successfully a solution of arsenic which consists of 1 Gm. (15 grains) arsenic trioxide and 2.25 c.c. (36 minims) normal soda solution in 100 c.c. (3½ ounces) of distilled water, representing a 1 per cent. solution of sodium arsenite, a solution which is very slightly alkaline. Its hypodermic use does not cause more inconvenience than an injection of morphine, while its intramuscular injection is painless. Lately the writer has used the intramuscular method (*glutei*) exclusively and has never seen the slightest tendency to supuration. The skin before injection is disinfected with an alcoholic solution of iodine and potassium iodide, and the site of injection is sealed with a mixture of this iodine solution, 1 part, to 4 of tincture of benzoin. A. Hertzfeld (*Jour. Amer. Med. Assoc.*, Feb. 25, 1911).

Herxheimer's reaction appears not only in the secondary stage of syphilis, but also, less strikingly in the primary and tertiary stages. The chancre becomes congested after the first arsenical injection and yields a copious serous discharge before undergoing retrogression. In the ter-

tiary stage similar reactions are observed, *e.g.*, in gummata, in tabetic oculomotor paresis, in laryngitis with stenosis, in specific myocarditis or nephritis, etc. Lacapère (*Presse méd.*, May 13, 1918).

Another therapeutic use of arsenic was introduced by Lombroso as a result of studies conducted by Coletti and Perugini, viz., in **pellagra**. Though it cannot be regarded as a specific, it is nevertheless efficient in many cases.

Lombroso used it in the form of Fowler's solution in dosage of 5, 10, 15, 20, and 30 drops (0.3, 0.6, 0.9, 1.2, 1.8 c.c.), or in the form of pure arsenous acid (arsenic trioxide) dissolved in slightly alcoholized water, in doses of $\frac{1}{40}$ to $\frac{1}{20}$ mg. ($\frac{1}{2560}$ to $\frac{1}{1280}$ gr.), increasing, according to tolerance, up to 0.001, 0.002, or 0.003 grams ($\frac{1}{64}$, $\frac{1}{32}$, $\frac{1}{16}$ gr.) and very rarely even to 0.01 gram ($\frac{1}{10}$ gr.). The administration of the drug is suspended for a few days from time to time. He cautioned against certain dangers in its use, however, and mentioned as dangerous symptoms the appearance around the neck of an herpetic eruption, profuse salivation, anorexia, vomiting, diarrhea, palpitation of the heart, syncope, burning in the pharynx and stomach, headache, great muscular weakness, and bronchitis. C. H. Lavinder (*Public Health Reports*, Sept. 10, 1909).

The majority of cases of **pellagra** will at some time or other be benefited by arsenic. Early in the disease its action, when given in large doses, appears to be almost specific, whereas late, when extensive nerve degenerations have taken place, benefit is only to be derived, in the author's opinion, with small doses. In the earlier stages he has had the best results with soamin administered hypodermically, starting with 1-grain (0.065 Gm.) doses every other day and increasing up to 3 or more grains (0.2 Gm.) to the dose until from 75 to 100 grains (4.8 to 6.5 Gm.) have been given, followed by a period of rest for a couple of weeks, then another

course of the drug if necessary. For internal use he believes Donovan's solution to give results slightly superior to those of Fowler's solution. The method recommended by Babes, of using atoxyl hypodermically, arsenic trioxide internally in $\frac{1}{10}$ -grain (0.0022 Gm.) doses, and about 1 dram (4 Gm.) of a 2 per cent. arsenic trioxide ointment rubbed into the skin, would seem valuable in the early stages. Louis Leroy (*Southern Med. Jour.*, Mar., 1912).

External Uses.—The slow caustic action of arsenic has led to its free use for the eradication of superficial malignant growths such as **epithelioma**. In general, excision with the knife is to be regarded as the best course to be followed in growths of a papillomatous nature as well as in those which, though extending deeply, are small and of definite, regular outline, permitting of ready removal with but little disfiguration. Where, however, the growths are more superficial and less definite in their outline, many dermatologists countenance the use of caustics, and of these arsenic is among the most useful because it possesses to a certain extent the property of sparing normal tissues and limiting its effects to the morbid cells. In cases where operative excision is refused, treatment with arsenic is also justifiable. The application of Marsden's paste, consisting of 2 parts of arsenic trioxide to 1 part of mucilage of acacia, or of a mixture of the same ingredients in different proportions, has generally been followed with the desired result. A layer of paste being applied over the growth, a piece of dry lint is placed over it, overlapping the paste one-half inch all around. After ten minutes the overlapping lint is carefully cut away and the paste is allowed to dry. After two or three days poultices are applied at short

intervals until the redness and swelling present subside. A line of demarcation appears around the lesion, the skin ulcerates, and the fissure formed gradually extends until the epitheliomatous mass comes away. The result of the caustic treatment with arsenic is obtained more slowly than with other agents such as potassium hydroxide, and the pain is more prolonged, if less acute. Cases of poisoning due to its absorption from the skin have been reported, but the danger is not such as to interfere with its careful use.

Morphine and cocaine have been of only slight assistance in controlling the pain caused by arsenical paste in the treatment of **cancer**. The writer has found in orthoform a means by which the pain can be obviated. Equal parts of arsenic trioxide, gum acacia, and orthoform made into a paste are applied to the surface to be destroyed. The anesthetic influence of the orthoform lasts several hours, and the action of the arsenic trioxide is in this way rendered painless. W. P. Nicholson (*Atlanta Jour.-Rec. of Med.*, vol. i, p. 738).

Another efficient, though somewhat more troublesome, method of using arsenic is that of Czerny, who applies a solution of 1 part of arsenic trioxide in 150 parts of a mixture of alcohol and water in equal amounts. The first step in the treatment is thoroughly to cleanse the sore by vigorous rubbing or scrubbing, causing a moderate amount of hemorrhage. The surface is then well moistened with the solution,—previously shaken up,—and the preparation allowed to dry, preferably without dressing of any kind. A scab forms, over which the solution is applied daily, until the former loosens and is retained in place only by a few loose adhesions. These are divided, the scab removed, and a fresh application of the arsenical

solution made. If on the next day the resulting scab is thin, light yellow, and easily detachable, this indicates that the tissues no longer comprise any trace of cancerous growth. If, on the other hand, a dark-colored, firm and closely adherent scab again forms, the treatment must be repeated. The thicker the scab, the stronger the solution should be made for the second treatment, *e.g.*, 1 to 100 or even 1 to 80. When the desired result has been attained there remains a granulating wound, covered with a delicate white pellicle, which is to be dealt with on general principles.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

ARSENOPHENYLGLYCIN.

See ATOXYL.

ARTERIAL PRESSURE AND BLOOD-PRESSURE. See BLOOD-PRESSURE.

ARTERIOSCLEROSIS.—DEFINITION.—Arteriosclerosis, chronic arteritis, or, when the smaller arteries are involved, arteriocapillary fibrosis, is a condition characterized by an increase in connective-tissue formation accompanied by degenerative changes, necrosis, and calcification. These latter may be circumscribed or diffuse. The fibrous formation occurs chiefly in the outer coats and is referred to as *sclerosis*; the degenerative processes involve the intima mainly and are spoken of as *atheroma*.

SYMPTOMS.—It is generally accepted that pathological lesions of the blood-vessels are present in the great majority of people over 50 years of age, particularly males. The involvement may be of some small portion of the

cardiovascular system or of the entire system, a local change in the aorta or a widespread fibrosis of the smaller vessels. In consequence of the fibrous overgrowth and the degenerative processes occurring in the walls of the vessels there must be more or less interference with the proper supply of food reaching the tissues. There must then be found symptoms of disturbances of nutrition as well as of the primary underlying cause that brought about the fibrosis. Inasmuch as the blood-supply to the different organs of the body varies greatly according to the importance of the tissues, the symptoms of arteriosclerosis will vary also with the organ involved.

There are symptoms of arteriosclerosis which occur early, *i.e.*, while the progress of the disease can still be arrested. These symptoms are in relation with slight and variable troubles of the circulation. The arteries are less elastic, the contractility of their muscular coats is lessened, and as a result the regulation of the course of blood is imperfect. These phenomena may be persistent or may appear only as the result of labor or fatigue. Josué summarizes them as follows: 1. General, such as fatigue on slight exertion, accompanied perhaps by painful sensations, as in the case of a man who suffers from headache after a long walk. The expression is indicative of lassitude, or perhaps discouragement. Another condition is that of intolerance to certain substances, such as alcohol and tobacco. 2. Vasomotor, of the teguments of the face. The patients may be flushed, or, on the contrary, pale, and in some cases there is an instability of the vasomotor innervation. Some persons are pale in the morning and ruddy in the evening. 3. Nervous, shown in inaptitude for

work, modifications of character, headache, abnormal sensations in the limbs, with some difficulty of movement, neuralgic pains, vertigo, insomnia, neurasthenia, and the development of traumatic neuroses. 4. Loss of hearing. 5. Ocular troubles, such as the development of the arcus senilis on the cornea, thrombosis of the central artery of the retina, and spasm of the smaller retinal arteries. 6. Respiratory, a dyspnea induced by comparatively slight exertion, and a condition of emphysema, the true cause of which is not easily to be recognized unless its possible relation to arteriosclerosis is considered. 7. Epistaxis, which may be one of the first indications of the change in the arteries. 8. Edema of the legs, not very marked, in the absence of cardiac or renal disease. 9. Cardiac troubles, such as palpitation, sometimes associated with angina; in some cases a more or less marked tachycardia is met with. 10. Arterial overtension, continuous and persistent, is a good sign on which to base a suspicion of arteriosclerosis. 11. Renal symptoms, which may be those of great or little renal insufficiency.

According to Kompe premonitory symptoms, such as nosebleed, particularly in subjects over 40 years, sometimes give warning of the early approach of softening due to arteriosclerosis. Cardiac hypertrophy with aortic changes, tense radial artery, tortuous temporal arteries, are also early signs. Sclerosed blood-vessels always rupture in front of the thickened and stenosed portion of the vessel.

The three principal varieties of arteriosclerosis which concern the practitioner are, according to Fitz: 1. *Cerebral*, with symptoms of headache, vertigo, wakefulness, loss of memory, convulsions, and focal lesions due to arterial rupture, thrombosis, or embolism. 2. *Cardiac*, with symptoms of weak heart; and palpitation, bradycardia, or tachycardia, arrhythmia; angina, dyspnoea, cardiac asthma, Cheyne-

Stokes breathing, epileptiform attacks, unconsciousness, passive congestion of the various organs, and dropsy. 3. *Renal*, with signs and symptoms of chronic fibrous nephritis. As to treatment, after diagnosis is made, very little is to be done in the way of remedies. The chief benefit of early discovery is the opportunity to give warning to the patient of the necessity of a change of habits, of avoiding mental, moral, and physical strain upon the blood-vessels which already show signs of weakness.

Arteriosclerosis is without symptoms during the first 5 years, and often even without objective signs. Pain in the cardiac region, usually on exertion, is one of the earliest symptoms. It occurs sometimes also after meals, giving rise often to an erroneous diagnosis of gastric fermentation. Arteriosclerotics are sensitive to meat proteins while some are also sensitive to fish and egg proteins. The flesh of fowl is frequently tolerated. L. F. Bishop (Med. Rec., Oct. 9, 1915).

Early symptoms of arteriosclerosis are a slight shortness of breath on a slight exertion; headache, or a sense of pressure or fullness in the head; slight giddiness on assuming the erect posture quickly; dilatation of the venules in the malar region. A feeling of tightness across the chest may be an early sign, but more often it is late. Cerebral symptoms also may appear early, but are generally late. Another early sign, which may be almost the only one, is an irritating cough, that calls attention to the vascular system, or a sort of sigh, due to a feeling as though there was not room enough in the chest. Digestive troubles are common, as well as the frequent passage of large quantities of limpid urine of low specific gravity. A. Graham-Stewart (Pract., Apr., 1915).

Before taking up the symptoms in detail it may be well to give a brief description of the histology of the vessel and its physiology in relation to the carrying on of the circulation. Con-

cerning this Allbutt gives the following in relation to the general structure of the arteries: The arteries of the body may be roughly divided into large, middle size, and small; possessing three coats,—internal, middle, and external.

1. The *tunica intima*, or inner coat, consists, from within outward, of three distinct layers: (a) An endothelial lining, in contact with the blood, made up of delicate nucleated cells joined together by a cement substance, and arranged like a mosaic pavement. This endothelium, slightly modified in different situations, lines the whole cardiovascular apparatus, and its integrity is of the greatest importance in preventing the coagulation of blood in the living vessels. (b) A subendothelial layer of branched connective-tissue corpuscles with intervening cement substance. (c) A continuous layer made up of a felt-work of fine elastic fibers with small openings therein, the fenestrated membrane of Henle. This elastic lamina in the empty, contracted artery has the appearance of a crinkled, bright-yellow line.

2. The *tunica media*, or middle coat, consists, in the large arteries, of alternate layers of elastic fibers and unstriated muscle fibers arranged circularly. The larger the artery, the more does the elastic element predominate; whereas in the arterioles the muscular coat is, relatively to the size of the vessel, much better developed, and elastic tissue is not present. If we consider the dynamics of the circulation this difference of structure is at once explained; the larger arteries by their elasticity help to convert the intermittent force of the heart into a continuous pressure. The muscle of the small arteries, by a general tonic contraction under the control of the

vasoconstrictor nerves, maintains the peripheral resistance to the outflow of blood, keeping the arterial system always overfull, while the elastic-buffer action of the large arteries, continually tending to overcome this resistance, causes a steady flow through the capillaries.

3. The *tunica adventitia*, or external coat, consists of connective tissue possessing a large number of interspersed elastic fibers, together with blood-vessels, lymphatics, and nerves. The blood-vessels—*vaso vasorum*—serve to nourish the walls of the vessels; they probably enter the middle coat of the larger vessels. At any rate, it is not disputed that the *tunica media* is nourished by the blood of the *vaso vasorum*. The lymphatics are numerous, and in certain situations, as in the central nervous system, they form distinct perivascular sheaths. Vasomotor nerves run by the side of the *vaso vasorum*, and over many of the larger vessels important plexuses of nerves exist. Variations in the thickness of the outer coat in different situations in the body have been explained as adaptations to resist the pressure of joints, and visceral and muscular movements.

Vascular Symptoms.—From this brief mention of the normal arrangement one can better understand the pathological changes and their action in modifying the normal circulatory phenomena. In taking up the symptoms occasioned by variations in the blood-vessel wall we must take into consideration the blood-vessel at the seat of the change, other blood-vessels, the heart, and the tissues. As a result of arteriosclerosis there is a varying degree of elasticity of the blood-vessels, either in being increased, as in an aorta where the wall has become much thinned, or

in being diminished, as in those areas where the vessel has become rigid from the deposit of lime salts. If the rigidity has been increased there will be a greater resistance than normal to distention during the systolic increase of blood-pressure. If the rigidity is not marked the normal distention may be brought about as a result of an increased contraction of the left ventricle. On the other hand, the systolic contraction may be unable to cause any distention. If the healthy heart muscle is able to overcome the resistance there will be an hypertrophy of the left ventricle. As one of the chief characteristics of connective tissue is to contract, we will find that the lumina of the arterioles will become smaller and smaller. Consequently the blood-pressure will tend to increase with an accompanying increase in the hypertrophy of the left heart. Although this is probably not the entire explanation of the hypertrophy that occurs in arteriosclerosis, yet it is theoretically sufficient.

If the rigidity is due to a deposit of lime salts, as occurs commonly in the aorta, there may be no alteration in the heart if compensatory changes can take place in the peripheral circulation. As atheromatous and calcareous changes are commonly associated with old age, when the integrity of the myocardium is interfered with, the heart in such an involvement of the aorta will be flabby and somewhat dilated. This will also be accompanied by a fall in blood-pressure.

If the calcification has involved many of the peripheral vessels as well as the aorta there is then a resistance exerted that cannot be overcome by an increased heart's action. Consequently the left ventricle not only will hypertrophy, but

will dilate with, at the same time, a thinning of its walls. If the rigidity of the vessel wall as well as its elasticity be diminished, either generally or locally, dilatations of various extent will occur, the beginning formation of aneurisms. Such a lesion, however, is not of the greatest importance so far as the circulation is concerned. The only effect is to increase the capacity of the arterial system by an amount equal to the cubic contents of the aneurism, and thereby proportionately reduce the peripheral resistance.

As a result of the diminished elasticity of the vessel wall there is developed an increased tendency to rupture. This depends upon a failure of correspondence between the tearing stress exerted by the blood-pressure and the power which resides in the modified vessel wall to resist that stress. In calcification of the aorta the rigid vessel gives way, primarily because the tearing stress to which it is exposed is greater than that which the healthy vessel is called upon to withstand. The tearing stress being greater when the radius of the vessel remains unchanged, when the vessel is rigid as in calcification, than it is when the radius is increased, when the vessel is distensible as in health. In a saccular aneurism the tearing stress exerted by the blood-pressure is actually lower than in the vessel upon which the aneurism is seated, and diminished with enlargement of the sac. The wall, however, gives way because, thinned by pressure from within and from without, its power of resisting the tearing stress is diminished to a proportionately greater extent.

In consequence of the sclerotic changes, the lumina of the vessels may become more or less decreased and

bring about to a varying extent certain changes. The velocity of the flow of blood in the proximal and distal parts of the vessel may be diminished. The pressure in the proximal portion may rise, and the pressure in the distal portion fall. These changes will, however, be modified according as to whether the vessel involved has anastomosing branches or whether it be a terminal or end artery. If the collateral circulation is free, the nutrition of the tissues is unaltered. If the collateral circulation is poor, the nutrition of the tissues suffers. If the artery is terminal, local anemia is complete and bloodless necrosis ensues. If the artery is terminal, but regurgitation of blood from neighboring capillaries or veins takes place, the result is the formation of a hemorrhagic infarct.

The writer emphasizes the significance of nocturnal polyuria and a persistently low gravity, and the importance of not giving nitroglycerin tablets the moment there is hypertension, since the patient may require a high pressure to get the blood through his small inelastic vessels. H. F. Stoll (*Jour. Amer. Med. Assoc.*, Sept. 16, 1916).

When considering the symptoms it must be borne in mind that they depend largely upon the organ involved and upon the extent of the involvement. The disease may start as a defect of metabolism before the production of organic changes in the circulatory system, and some authors believe that there is a prodromal and curable stage of arteriosclerosis. A stage of toxemia causing spasm of the arteriocapillary system, increased peripheral resistance, increased functional activity of the heart, and increased pressure in the arteries; but not necessarily changes in the vessel walls.

Various nervous symptoms are to be met with in this disease, some of which are consequences of the disease, while others are due to associated organic diseases. Those who suffer with arteriosclerosis are often affected at the same time with structural disease of the kidneys, heart, brain, etc. The error must be avoided of attributing to arteriosclerosis the symptoms which result from purely accidental organic diseases when associated with it, but not essentially due to it. There is great danger of attributing all the obscure conditions of senility and even of the presenile period to arteriosclerosis. A. Stengel (*Amer. Jour. Med. Sci.*, Feb., 1908).

Tests of internal ear functioning in the diagnosis of cerebral arteriosclerosis were studied by the writer, who recorded 1026 cases. In most of these the ear disease overshadowed pathologic conditions elsewhere. Vertigo was the usual symptom. He found it possible by repeated examinations to detect and trace the progress of arteriosclerosis of the arteries of the brain through the manner of onset, the course, and the intensity of the phenomena presented by the ear rather than by the individual symptoms themselves. Tinnitus proved especially instructive; it occurred at intervals or continuously, but in the course of perhaps many years organic disease of the auditory nerve became manifest. Failure of all treatment of the tinnitus indicated actual organic injury in the domain of the auditory nerve. Stein (*Zeit. f. klin. Med.*, xc, 1-2, 1920).

In many instances there may be a widespread involvement without any disturbance of the general health of the individual, who may seem quite vigorous. The arteries will show an increased hardness, but no one organ may be sufficiently implicated to give rise to symptoms referable to it. The patient may be able to carry on his work, both mental and physical, most satisfactorily, but the discovery of his condition may be most fortunate in that

he can guard against a mode of living that would tend to increase his arterial degeneration. Such a case may show an increasing pallor, an anemic appearance due rather more to a loss of coloring matter of the blood than to an actual deficiency in the number of red corpuscles. There is generally a gradual loss of power, both physical and mental, or at times nothing may have been noticed till the patient suddenly breaks down.

At this time the peripheral vessels will be found to have become hardened and somewhat tortuous, the blood-pressure will be in the neighborhood of 200 mm. of mercury, cardiac hypertrophy may be noticeable, and some casts and albumin be present in the urine. There will usually be a history of neurasthenia, the patient being irritable and suffering from insomnia. Although such instances of general involvement are encountered, as a rule quite definite types of the disease can be constructed according to the predominance of certain symptoms indicating involvement of special organs.

In 12.3 per cent. of 98 cases of arteriosclerosis examined by Sawada, increased blood-pressure, usually within 130 mm. to 160 mm., was noted. Two-thirds of the cases with increased tension were associated with an accentuated second aortic tone. However, there was more frequently an accentuated second aortic without increase in tension. A constant blood-pressure over 170 mm. suggests the existence of a chronic interstitial nephritis, even if albumin be absent from the urine.

Among 420 patients (not including any cases with loss of compensation on part of the heart) examined by Dunin, 120 gave evidence of normal or diminished pressure. Some of these patients were not aware of their vascular lesion and complained of only few symptoms referable to it, but in the great majority angina pectoris, arrhythmia of the pulse, dyspnea, and swelling

of the feet were present. He divides cases with increased tension in arteriosclerosis into several groups: (a) Those without subjective symptoms, constituting about 30 per cent. The usual complaint was here referable to nervousness, obesity, or renal or biliary calculi. Some of the severest cases (240 to 290 mm. pressure) belong to this category, and the absence of symptoms can only be explained by a healthy condition of the heart, which was able to overcome increased resistance in the capillaries. Accentuation of the second aortic sound and a systolic aortic murmur were common. (b) In this group the subjective symptoms were slight or very marked, but the kidneys were usually affected. (c) Here angina pectoris was very common. Angina is much more common with low pressure, but no difference between the two forms concerning general course or prognosis could be detected. The lowest figures obtained (65 mm.) were in cases of angina, and during the attack the pressure often fell 30 mm.

EDITORS.

In many cases of even well-marked arteriosclerosis the blood-pressure is not raised. This may be due to localization of the disease to a part of the arterial tree or to the fact that the heart may be giving up the struggle, the once high pressure having fallen. In many cases of arteriosclerosis the blood-pressure is above normal. In a given case in which the pressure is raised it cannot be assumed that it is high because of the disease of the vessel walls, nor that the sclerosis is due to the increased pressure. The arterial stiffening may be due to syphilis and the hyperpyrexia to some intercurrent condition of nervous or toxic nature which may be removable by suitable treatment. Rudolf (Amer. Jour. Med. Sci., Sept., 1908).

The writers have observed in patients in whom the blood-pressure is high that the pupil is larger than the average normal pupil, with a usual minimum of 4.5 mm. in width. While it contracts promptly to light stimulus, it immediately returns to the original size and there remains, without the light stimulus having been changed. The association of this

symptom with the high blood-pressure of arteriosclerosis is so nearly constant as to make it at least strongly suggestive. Wiener and Woldner (Jour. Amer. Med. Assoc., July 17, 1915).

Out of 44 cases in which a gross cerebral vascular lesion had existed, 31 exhibited evidence of retinal vascular disease, while in 19 of these they were severe. In 26 cases of 27 that died, a gross vascular cerebral lesion proved to be the cause of death in 12. R. F. Moore (Quarterly Jour. of Med., Oct., 1916, Jan., 1917).

These local manifestations can be considered under three headings: (1) cardiovascular symptoms, (2) nervous, and (3) renal. Sometimes the pulmonary symptoms may be prominent.

Cardiovascular Symptoms.—In the first stages, owing to the increased peripheral resistance, a pure hypertrophy of the left ventricle occurs, and of the right ventricle to a less and variable degree. The area of cardiac dullness is increased and the impulse is displaced outward and slightly downward. There may be reduplication of both first and second sounds, and the latter over the aortic cartilage is accentuated and possibly roughened. In a considerable number of cases the insufficiency of the aortic and mitral lesions is due to a process in the leaflets similar to that which is going on in the vessels. The hypertrophied cardiac muscle may undergo various changes due to the interference with its nutrition. This diminution is due to the increase of the resistance to be overcome and the involvement of the nutrient vessels of the heart by the degenerative processes. So that although the heart has more work to perform, the quality and quantity of the blood-supply have suffered. In consequence of this there will appear parenchymatous, fatty, and fibrous

changes in the myocardium. As this occurs there will be more or less dilatation of the ventricle. The patient will begin to complain of palpitation, dyspnea, and shortness of breath on exertion. During such attacks the apex beat will usually be forcible and the pulse one of high tension. A mitral murmur appears, the veins are obstructed, the urine becomes scanty and high colored, and dropsy, gradually increasing in extent, appears. This latter condition is probably due to alterations in the vessel walls, to an increased amount of fluid within the vessels, and to the weakening of the cardiac muscle. In consequence of the diminution of the lumen of the coronary arteries or their branches by the sclerotic changes, the amount of blood that gets to the myocardium will be decreased. The dyspnea increases until the patient is constantly struggling to get the slight extra amount of air that seems needed to relieve him. The signs of dilatation of the heart become more marked; the apex beat becomes diffuse and develops a gallop rhythm, which on auscultation may be heard over the entire heart. Accompanying this there may be a systolic sound. As a rule, not very much can be done, as the entire cardiovascular system is involved. Occasionally by means of proper treatment the condition may be greatly improved so that the patient can resume his work. An individual may suffer from numerous similar attacks and have intervals of comparative comfort before the condition terminates fatally.

The rigid vessels in arteriosclerosis are unable to compensate the emotional changes in the heart rate, and consequently the radial pulse reflects them. Any fluctuations in the diastolic blood-pressure of psychic origin which amount to more than 15 per cent. of the

systolic fluctuations testify to the presence of arteriosclerosis. Schrumph and Zabel (Münch. med. Woch., Sept. 12, 1911).

Cardiac inefficiency should be given its full value as means of early diagnosis and as an indicator for therapeutic initiative. The great usefulness of test doses of digitalis with or without reinforcement by physical rest constitute the very foundation of timely diagnosis. C. L. Greene (Amer. Therap. Soc.; Med. Rec., Sept. 23, 1916).

Associated with the changes of the heart muscle are, as mentioned above, the degenerative processes involving the coronary arteries, particularly a sclerosis. This usually occurs about the orifices, although the main branches or the smaller ones may be affected. This condition may occur uncomplicated by valvular lesions, and in young men may be out of all proportion to the changes in the other vessels. As a result of this one of the most important symptoms is that of *angina pectoris*, which would seem to occur particularly in those cases where there is an increased peripheral resistance, and not in mere stenosis of the coronaries without the increase. (See also the article on *ANGINA PECTORIS* in vol. i.) The same condition may be brought about by involvement of the main branches. In those cases where sudden death has taken place thrombosis of one of the branches has probably occurred, and the heart muscle will show a fibrosis or a small anemic infarct with an extensive fatty degeneration. Under ordinary conditions the decreased supply of blood to the heart may be sufficient to enable it to carry on its functions, but if some sudden demand is made upon the myocardium it is unable to meet the situation. There is a temporary local anemia, and the heart muscle, which is

particularly susceptible to a decrease in the amount of oxygen, will contract spasmodically, giving rise to the extreme pain that accompanies such attacks. The same muscular cramps will arise in other parts of the body where the nutritive vessel is thickened and a sudden excessive demand is made.

Of the other changes resulting from the sclerosis, *aneurism* is one of great importance. The mechanism of their formation will be taken up in detail later. These dilatations may vary greatly in size, from those extensive ones involving the larger vessels to the miliary type such as are found in the vessels of the brain, the symptoms occasioned depending not only on the size, but also on the location. When located in the brain, rupture may take place at any time, giving rise to hemorrhage of varying extent.

Involvement of the *peripheral vessels* may give rise to various local disturbances according to the degree of the sclerosis. When there is a sclerosis of the arteries the disease advances progressively, and as this takes place there must necessarily be an interference with the nutrition of the body in general and frequently of certain organs in particular. As the muscular and elastic elements diminish there is an increase in the amount of connective tissue, and at the same time there is more or less atrophy of the parenchymatous portions of the tissues.

A condition of the *muscles* of the extremities, similar to that of the cardiac muscle in *angina pectoris*, is quite common in old people in whom the vessels have become sclerotic. On account of the interference with nutrition the muscles very frequently undergo spasmodic contractions accompanied by severe pain. If the sclerosis is more

marked there may be considerable atrophy of the part accompanied by various forms of degeneration. In advanced cases the blood-supply may be so interfered with as to produce senile gangrene. This form is usually limited to a single limb, or, if it affects more than one extremity, the lesions are successive in order. As a rule, the lower limbs are the more commonly involved. The lesion is generally quite extensive, implicating a whole toe or a part of the foot, and tends to spread to an indefinite degree. In these cases there may be a greatly diminished pulsation or it even may be obliterated.

Under the heading of *nervous disturbances* in arteriosclerosis come many varied symptoms. These may be due in part to the associated lesions of the different organs. The sudden occlusion or obstruction of a larger peripheral artery, either experimentally by pressure applied from without or pathologically by an embolus within, gives rise to quite characteristic symptoms. There is usually a sudden onset of pain, frequently very violent, and a loss of power in that part supplied by the obstructed vessel. The pain may subside in a short time to be renewed if secondary emboli occur, but later the extreme pain lessens and becomes a continuous aching. Sometimes sharp pains may radiate from the point of obstruction. As a rule, the accompanying loss of power is only partial, but may become complete, as frequently happens in embolism of the abdominal aorta, causing complete obstruction. In addition to the pain there may be pallor, coldness, tingling or numbness, weakness or complete cessation of the peripheral pulse; occasionally violent cramps.

Cases of muscular cramp may be set down to arteriosclerosis, according to

Rohde. In these cases the diagnosis is often, if not invariably, made by the nature of the palliative remedy.

Case in which a man suffering from arteriosclerosis had attacks of a feeling of oppression in the chest and cramp-like pains with a numb feeling, which extended from the angle of the lower jaw on each side to the top of the shoulder, and then on the left side down the radial side of the arm and forearm to the thumb and index finger, with almost complete loss of movement of the muscles of the left arm. In addition to this any attempt to use the left arm excited the same symptoms, to a less degree, as were present in the attacks. Bretschneider (Berl. klin. Woch., May 8, 1911).

If a collateral circulation does not become established, gangrene is the usual result. In other cases where the arterial obstruction is less marked than in the above, there may develop such symptoms as coldness, numbness, tingling, darting pains, and finally extreme suffering. From a study of the matter it would seem unnecessary that there should be a neuritis present to account for the pains. Thoma lays considerable stress upon the pain in angiosclerosis, which he says is generally put down to rheumatism. As the basis of the pain he has demonstrated the presence of Pacinian corpuscles in the walls of the vessels. Again, there may be cases in people of advancing years with symptoms similar to the above, and in addition suffer with a stiffness or weakness of the extremities, with a sense of coldness, or of heat, or of some form of paresthesia. These symptoms are more common in the legs than in the arms. The severity of these manifestations may have a direct relation to the degree of arteriosclerosis, and may increase in direct proportion with the advance of the disease. In other cases it may be

observed that the symptoms increase and decrease as the condition of the heart suffices or fails to maintain the circulation in the sclerotic vascular system.

Four cases in which hypertension, arteriosclerosis, and hypertrophy of the vesicle were accompanied with rhythmical movements of the head, the movements being up and down and from left to right. These oscillations closely simulated true pulsations, being composed of an abrupt vertical ascent and a like vertical descent, followed by secondary oscillations of minor amplitude, and the principal ascent was synchronous with the carotid diastole. M. Bucco (*La Riforma Medica*, Feb. 25, 1903).

The vascular crises of arteriosclerosis are described by the writer. They may occur in the brain, the chest, the abdomen or in the legs, the latter with intermittent claudication. The chest group comprises angina pectoris and acute edema of the lung. Abdominal crises occur after physical exertion or emotional stress, and seem to be independent of the meals. In the cerebral group there may be attacks of sudden unconsciousness for a few minutes, but no convulsions. The pallor is followed by vasodilation and sweating as consciousness returns. In a case described, these attacks return every 3 or 4 weeks. B. L. Duran (*Progresos de la Clinica*, July, 1918).

Mention may also be made of a large group of more or less painful affections of the extremities associated with arterial disease, in which the symptoms suggest the intervention of spinal or reflex vasomotor conditions between the arteriosclerosis and the acute manifestations. Among these are: erythromelalgia, Raynaud's disease, "dead fingers," and intermittent claudication. All of these conditions occur in persons who have more or less decided arterial disease. In the first three the nature of

the attacks and paroxysmal character of the vasomotor phenomena suggest that reflex nervous influences play an important part, but the association of marked arteriosclerosis and the constantly recurring circulatory disturbances suggest that the reflexes have their origin in the arterial disease.

So far as *intermittent claudication* is concerned, this peculiar manifestation has been generally accepted as being due to arteriosclerosis. The symptoms do not differ from those already referred to, but the pains, paresthesia, stiffness, cramps, and weakness are distinctly the result of effort. Some hold that these symptoms result directly from the inadequacy of the blood-supply when the muscular effort makes greater demand upon the circulation. Others have thought that vasomotor spasm results from the exertion and causes the symptoms. In proof of the first of these views it has been shown that painful cardiac attacks associated with coronary disease lessen when the myocardium has grown considerably sclerotic. In consequence of which the need of active circulation is less imperative than in the case of a more normal heart muscle. Others maintain that a nervous element plays a part by exciting vasomotor spasm, and in proof of this cite the facts that coldness, pallor, and weakness of the pulses are frequent symptoms of the attacks, and that claudication is especially likely to affect arteriosclerotic people who have a general neurasthenic condition as well. On the other hand, it is significant of the purely obstructive character of the vascular trouble that claudication has been universally recognized as a forerunner of gangrene. In erythromelalgia the red, painful neuralgia, arteritis

obliterans, has been found in many cases.

Early differentiation of arteriosclerosis of the central nervous system is essential, as proper treatment may arrest the trouble and ward off social and material loss. When headache occurs and persists, with occasional vertigo, the possibility of arteriosclerosis should be suggested. The dizziness in these cases is extreme, and unless the patient can catch some support he may fall. It is important to exclude vertigo from an ear affection and from varieties of true nervous vertigo. When due to arteriosclerosis, the memory for recent events is liable to suffer. The patients lose the thread of their discourse, forget the number of their room in the hotel, figures, and names; they get into the habit of noting down whatever they wish to remember. A tendency to facile emotions and irritability may also be observed. Cramer (Deut. med. Woch., Sept. 16, 1909).

Largely as a result of the anemia of the brain and the consequent interference with nutrition there are certain *cerebral manifestations* of arteriosclerosis. Many of these conditions are in all probability due to partial thrombosis of larger cerebral vessels or to complete thrombosis of smaller branches. Partial thromboses of the larger vessels are seldom absent in cases of extensive arteriosclerosis of the circle of Willis. These thrombi cause a rather rapid encroachment on the lumen of the vessels, and thus interfere with the circulation in a manner more abrupt and violent than does the narrowing of the lumen from increase of the arterial disease itself. Of the early symptoms headaches of a distressing character are frequent. As a rule they are associated with an increase in arterial tension and are commonly relieved if the pressure be reduced. Usually frontal and continuous, they occasionally may be

paroxysmal, resembling migraine. Another symptom commonly present is vertigo, generally transient, but most distressing. It is often brought on by a change of posture from sitting to standing, emotion, sudden exertion, etc. This deprives the brain of the proper amount of blood and hence causes the symptoms. In other instances the vertigo may be associated with epileptiform seizures as a result of the disease of the cerebral arteries. Such patients have attacks of dizziness, headache, twitching of the muscles, and extreme weakness. In some, compression of the carotid arteries will cause the symptoms to appear. The resemblance to petit mal may be quite marked. These attacks may be accompanied by momentary loss of consciousness or bewilderment, followed by slight clonic convulsions affecting the arms and legs, but not beginning in any particular member and ending with a period of mental confusion and aphasia lasting from a few minutes to an hour. There may also occur transitory disturbances of function of parts of the brain or cord, leading to hemiplegia, monoplegia, aphasia, or even paraplegia. Recovery from an attack is commonly complete, and the patient is able to go about his daily affairs as usual. Again, the attack may appear in the form of coma and stupor, which can continue for hours or even days, with ultimate recovery. The cause of these doubtless may be an incomplete uremia in some cases, or other form of toxemia, but the sudden relief of symptoms that so often occurs is evidence that they are more usually dependent upon the condition of the cerebral circulation.

One of the commonest symptoms of cerebral arteriosclerosis is a gradual failure of the mental powers. An indi-

vidual no longer shows the same interest in his affairs, becomes careless and apathetic, his memory and judgment are at fault, the facial expression is dull, and, progressing month by month, that at last the psychical powers are so reduced that the individual is in a state of dementia. These indications of mental degeneration are, however, not often seen as a result of arteriosclerosis in men under 40 years of age. It is common enough as presenile change in men at or about 60. Rupture of the cerebral arteries leading to apoplexy and thrombosis in consequence of changes in the intima are common events in arteriosclerosis.

Psychoses of various forms may make their appearance. The patient becomes dull, develops an uncertain temper; there may be present delusions, imperfect orientation, weakness of intellect; speech is often slow and slurred. There may also occur tremors, differences in the pupils, and exaggerated reflexes. Delusions of grandeur are not common.

A number of the patients studied by the authors stated that the headaches from which they had formerly suffered had lessened or disappeared of late years. The comparative immunity from headache was the more notable in view of the fact that signs of renal degeneration were present in 36 per cent. of the cases and the blood-pressure averaged high. The apoplectiform or claudication attacks are, moreover, not necessarily indicative of serious organic disease, as a case which was reported by the writers shows, and they are inclined to credit them to cerebral fatigue with temporary suspension of function rather than to actual changes in the vessels. G. L. Walton and W. E. Paul (Jour. Amer. Med. Assoc., Jan. 18, 1908).

Certain cases symptomatologically described as melancholia, hypochondria,

neurasthenia, etc., may be better grouped on etiological grounds as cases of arteriosclerotic brain disorder; while the arteriosclerosis is an important factor, the factors which led to the symptomatological grouping are not to be neglected. This necessitates the analysis of the depressions in advanced life.

The neurological picture in advanced cerebral arteriosclerosis is still ill defined, and for the differential diagnosis of the various organic dementias further clinical material is required. In certain cases of epilepsy with onset in late life, the convulsions and general symptomatology are closely related to arteriosclerosis. C. Macfie Campbell (Amer. Jour. of Insanity, Jan., 1908).

Many of the subjects are the offspring of gouty or arthritic parents, and in these the premonitory signs of the degeneration may be observed quite early in life in the form of attacks of nose-bleed, migraine, premature baldness, etc. There is a slackening of the intellectual powers, and the subject is easily fatigued. There is a peculiar sensitiveness to alcohol and tobacco, even in reduced quantities. Irritability of temper is fairly constant. More or less persistent headache is a common early feature. It is apt to be caused or intensified by intellectual effort, by alcohol, or by excitement.

Sensory disturbances, in the form of neuralgia or giddiness, are fairly common. The same is true of disturbances of sleep, but true insomnia is rare. Mental depression is always present to some degree. Gubb (Lancet, July 11, 1908).

After a study of the psychoses associated with cerebral arteriosclerosis, the writer concludes that there are 3 periods of development: (1) the *involuntary*, where degeneration is caused by the ordinary wear and tear of life; (2) the *toxic*, in which degeneration is caused by poisons of acute and chronic infections and intoxications; (3) that in which degeneration follows *persistent high blood-pressure*. Nack (Med. Rec., Dec. 11, 1915).

Abdominal symptoms may be quite prominent in the form of epigastric

pain and intestinal cramp, associated with high blood-pressure and shock of greater or less degree.

The most characteristic feature according to Rodhe is the strict localization of the pain in the epigastrium, appearing in persons of 40 or over. The pain is a sharp, stabbing or burning sensation, lasting generally only for a few minutes. It radiates sometimes to the liver, shoulder, or arms, and ptalism may be observed with a cold sweat and semiunconsciousness. Between the attacks there is no pain, at least in the milder cases; in others there may be a dull, continuous ache. There are generally no other disturbances from the digestive tract, although sometimes constipation, diarrhea, meteorism, etc., may be observed. Other morbid processes are liable to occur in the digestive organs aside from those due to the arteriosclerosis, of course, and the latter may induce thrombosis, or even actual ulcer formation. The attacks may follow unusual physical exertion. Buch has reported a case in which the attacks were liable to come on when the patient lay down. Emotions and excesses are also liable to bring on an attack. On the other hand, the kind of food has no influence. The shortness of the painful attack, the radiation of the pains, and the occasional alternation with angina pectoris confirm the diagnosis. The same causes that elicit angina pectoris are noted in the history of these attacks. Pressure on the epigastrium sometimes induces pain similar to that of the typical attack. The pure arteriosclerotic gastralgia subsides or vanishes altogether under diuretics, digitalis, or strophanthus. The syndrome may simulate ulcer, nervous dyspepsia, or

even cholelithiasis, until death in syncope occurs and autopsy reveals the unsuspected sclerosis of the coronary, stomach, or intestinal arteries. Jaworsky has published reports of 4 such cases in which the patients succumbed suddenly.

Abdominal arteriosclerosis may be attended with annoying flatulence, painful distention, especially in the right hypochondrium, and occasional colic and eructations, the latter sometimes bringing relief. The patients are irritable, and sleep is broken and fitful. Sometimes the condition in the night is improved if the patient eats something. The appetite is good, with a tendency to constipation. The stomach digestion is generally good, with occasionally a little hyperchlorhydria. Some patients in this class have proctitis with considerable secretion, eczema of the anus, and hemorrhoids; slight albuminuria may also be observed. Gradually the pulse rate increases and a systolic murmur becomes audible sometimes, with accentuation of the second aortic sound; the blood-pressure rises, and the diagnosis of arteriosclerotic disturbances is rendered certain by an attack of angina pectoris. Some of these conditions may exist for years and deceptively simulate nervous dyspepsia. The patients are generally men who have been subjected to overwork. Rosengart (*Münch. med. Woch.*, Bd. liii, Nu. 20, 1906).

Series of cases of abdominal arteriosclerosis in which the sclerotic condition of the abdominal vessels caused violent painful spasms in the abdomen, due to spasmodic contraction of the vessels of the intestines and the resulting local rise in blood-pressure. The pains are probably located in the sympathetic and the mesenteric plexuses. Besides the anatomical changes in the vascular apparatus, functional disturbances, as from the influence of nicotine and other poisons, are liable to induce such spasms. Differentiation is frequently difficult and seldom possible until after prolonged observation. The diagnosis is aided by the prompt benefit generally

derived from drugs which act on the vascular system. Perutz (*Munch. med. Woch.*, Bd. liv, Nu. 23, 1907).

Arteriosclerosis of the stomach may occur in the young, may cause fatal hematemesis or merely prolonged melena, and may occur independently of general arteriosclerosis. The diagnosis is generally difficult. Lewin (*Archiv f. Verdauungskrankheiten*, April, 1908).

In the gastrointestinal disturbances of arteriosclerosis the symptoms are generally, first, abdominal pain, paroxysmal in the beginning, later becoming continuous, and next to this in frequency is weakness and sometimes loss of weight, the latter being due, in part, to the dieting for the dyspeptic symptoms. Abdominal distention and belching are often present, and the association of dyspeptic symptoms with weakness and loss of weight may cause suspicions of malignant gastric disease. The appetite may be normal, increased or decreased, and the bowels variable. Gillbride (*Jour. Am. Med. Assoc.*, Mar. 20, 1909).

The symptoms of abdominal arteriosclerosis are paroxysmal pains in the stomach region or elsewhere in the abdomen, especially around the umbilicus, and tympany. The attacks occur independently of the intake of food, but are elicited by the factors which experience has shown induce symptoms in heart and vascular affections. Again, the abdominal angina is most liable to develop when the patient reclines. It is more common in men than in women, and most of the patients are over 40 or 50 years old. Kreuzfuchs (*Deut. med. Woch.*, Feb. 17, 1910).

Case in a heavy smoker 52 years old who complained of an extremely sweet taste. There was also a sensation of oppression with dyspnea on exertion. The heart was hypertrophied to the left; there was accentuation of the second aortic sound and a blood-pressure of 175 mm. mercury. The diagnosis of arteriosclerosis was beyond doubt. Another case of undoubted arteriosclerosis suffered from periodic attacks of pain in the tongue. A. Müller (*Zentralbl. f. innere Med.*, Nos. 28 and 29, 1911).

There are two varieties of intestinal arteriosclerosis: atheroma of the mesenteric arteries, long neglected, but now recognized as common, and arteriosclerosis properly so-called of the arteries of the intestinal wall. The former generally accompanies chronic aortic disease in syphilitics who have passed the fiftieth year. The latter is seen in younger subjects of alcoholism, lead poisoning, syphilis, typhoid, or gout. Pain is the most striking symptom, coming on most severely after an effort, mental or physical, and referred to the umbilical region or to the loins. There may be retching, meteorism, and nausea. Rest gives relief, but several attacks may supervene in one day. The pain is probably due to irritation of the nerve branches of the intestinal sympathetic, through sclerotic lesions of the vasa nervorum. Some writers, however, refer the pain to lesions of the abdominal aorta. Lagane (*Presse méd.*, Dec. 13, 1911).

Though rare, arteriosclerosis of the abdominal vessels may induce symptoms suggesting angina pectoris, gastric trouble or attacks of meteorism. J. A. Hedlund (*Hygiea*, lxxvii, No. 9, 1915).

The vessels of the pancreas may show an extreme involvement, as is frequently the case in regard to the spleen. Sclerotic changes in the uterine vessels may give rise to marked disturbances. Infarcts may occur or there may be hemorrhages from the endometrium. This latter type usually occurs after the menopause and, as a rule, has to be treated by hysterectomy.

A diagnosis of arteriosclerosis of the uterus can only be made where it is possible to exclude every other cause of hemorrhage from the uterus, and by microscopic examination of scrapings from the uterus in which sclerosed capillaries are found, or finally from sections of such a uterus after its removal. Arteriosclerosis as a definite cause of hemorrhage from the uterus appearing in women between the ages

of 40 and 50, and among those who had borne children, is of greater importance than has generally been determined. In a fair proportion of cases the hemorrhages from the uterus are in themselves sufficient to endanger the life of a woman and can be made to yield only to hysterectomy. C. M. Rees (Surg., Gynec. and Obstet., Nov., 1908).

Impotence from arteriosclerosis due to cavernositis chronica, sclerosing inflammation of the corpora cavernosa, is not generally recognized. The patient, above middle age, complains of curvature of the penis during erection until coitus becomes impossible. Syphilis, alcohol, rheumatism, and gout are the chief etiological factors, though it is difficult to explain why the pathological process should localize itself in the penis. Whatever the primary etiological factor may be, the penile process is merely the local expression of general arterial disease. In these cases cardiovascular changes are found. Arcus senilis may be present, or the marked signs of hypervascular tension. The prognosis is unfavorable so far as disappearance of the deformity is concerned. G. F. Lydston (Med. Fortnightly, May 11, 1908).

Some loss of functional power of the uterine muscle is the predisposing cause of bleeding in cases of arteriosclerosis. This loss of functional power is due either to the development of fibrous and elastic tissue from subinvolution or to the condition which caused this subinvolution. Chalfant (Jour. Amer. Med. Assoc., Jan. 28, 1911).

Renal Symptoms.—As many of the associated symptoms in general arteriosclerosis are due to renal involvement, lesions of this organ will be dealt with separately. This lesion of the kidney is responsible in a large percentage of cases for a considerable elevation in blood-pressure. This elevation is, however, definitely connected with arterial spasm in general, and may involve organs other than the kidneys. There may be found a small, contracted kid-

ney associated with an extreme grade of arteriosclerosis which may be regarded as secondary and due partly to the high pressure and partly to toxemia. The true kidney of arteriosclerosis, however, is a red, beefy organ which is firm, hard, and dark in color, not at first reduced in size, sometimes, indeed, slightly enlarged. Very often with this kidney there may be few or no urinary symptoms. In a late stage there may be found large, flat areas of atrophy of the cortex, or a large section of one organ may be involved in consequence of an obliteration of the arteries passing to the part. The urine in these two groups presents striking differences. In the small, contracted kidney the amount is increased, the specific gravity is very low, the albumin small in amount, often absent in the morning, hyaline casts are present, and very often red blood-cells as well. The urine of the arteriosclerotic kidney may contain at first no albumin, or, if present, the amount is not large; the specific gravity is normal or sometimes high. Later, the albumin may be present in large amount, and sometimes, as when a patient is admitted with an attack of cardiac dilatation, the urine is scanty, usually containing a large amount of albumin and numerous tube casts due to an intercurrent nephritis. In consequence of the renal changes there may appear many symptoms indicating a special involvement of this organ by the sclerotic process.

The arteriosclerotic kidney is a local phase of general arterial disease, producing in the kidney just the alterations which it produces in other organs of the body—alterations which need not amount to anything very grievous, as they are compatible with many years of life; but granular kidney, on the other hand, is some form of progressive in-

inflammation of the gland as such, the structure essential to its function being attacked. In this fatal disease arteriosclerosis appears in two ways—primarily and essentially in the fine arterioles of the organ itself; secondarily and later in the systemic arteries, as the effect of strain under the excessive arterial pressures in which granular kidney is always and regularly involved. Sir Clifford Allbutt (Brit. Med. Jour., April 22, 1911).

In a series of experiments on the functional capacity of the kidney, the writer found that after taking water normal kidneys excrete it all, arteriosclerotic patients about one-fourth. Normal kidneys excrete most at 8 A.M., arteriosclerotic patients later. He concludes that there seems to be a close relationship between arteriosclerotic kidneys and chronic kidney disease. Olaf Scheel (Med. revue, Nov., 1911).

The earliest manifestations are usually a hardness of the pulse or a slight edema. Dropsy, however, may be totally absent for a long time or altogether, particularly if the heart be much hypertrophied and little dilated. Occasionally there may be a good deal in the later stages, especially when the hypertrophied heart has become dilated so as to permit of regurgitation through the mitral orifice. This may be accompanied by a definite mitral murmur, though the valve flaps may be perfectly healthy. In such a case there may be pulmonary apoplexy with hemoptysis, and the dropsy may take on many of the characteristics of that of cardiac origin, which, indeed, it partly is. It may become considerable and general and affect not only the legs, but the pleura and peritoneum. Vomiting and various forms of gastric disturbances may be present. Many inflammatory affections may appear; bronchitis is exceedingly common; pneumonia and

pleurisy are frequent, as is pericarditis. The brain is also involved, particularly when the kidneys are becoming insufficient to carry on their work, and symptoms of uremic poisoning appear. The patient sometimes becomes restless and irritable; in the advanced stages transient delirium or temporary mental failure with delusions may occur.

Of the symptoms resulting from renal deficiency that of *uremia* is the most alarming. Although many theories have been advanced, its cause is still unknown. A comparatively recent theory is that of Ascoli, who attributes uremia to nephrolysins. It has been shown that when cells of a particular organ are injected subcutaneously or into the peritoneal cavity, substances antagonistic to the special cells injected are found in the organism. When broken-up renal substance is injected into animals, substances are found in the serum of the animals so treated which exert a destructive action upon the renal cells of other animals. When injected into a second animal such a serum sets up a nephritis and causes albuminuria, and the serum of the second animal, when injected into a third, has been found to excite a temporary albuminuria. It has been suggested that the tendency to chronicity in renal disease is due to the establishment of a vicious circle. That the nephrolysins formed as a result of the renal lesions aggravate the morbid condition in the kidneys. There is also evidence to show that the effects of cytolsins are not confined to the special tissues to which they are antagonistic, but may be more widespread. It, therefore, may be that the phenomena of uremia result from the action of nephrolysins upon the nerve centers.

Inasmuch as the character of the uremic manifestations is so strongly suggestive of a toxic origin, investigators have, for the most part, sought to explain them as the results of the accumulation in the blood of a poison or poisons. The obvious association which exists between uremia and deficient functional activity of the kidneys naturally suggested that the toxic material might be found among the end products of metabolism, which it is the function of the kidneys to secrete. No substance, however, among the normal excretory products has been found that will cause the symptoms observed. Consequently many hold the view that the manifestations are due to some intermediate product of metabolism.

One of the later symptoms of uremia is uremic asthma. In such cases the patient, whose breathing at ordinary times is normal or nearly so, may be suddenly seized in the early part of the night with agonizing dyspnea. The attack is like one of bronchial asthma with cardiac additions. There is an extreme want of breath with violent inspiratory effort and urgent orthopnea. There is much palpitation and cardiac distress and apprehension. After an attack lasting perhaps a couple of hours, the difficulty yields with wheezing, coarse crepitation, and the expectoration of frothy fluid. This is sometimes blood tinged or accompanied with separate sputa containing bloody mucus. The dyspnea and distress subside, the respiration resumes its former tranquillity, and nothing remains of the paroxysm except the prostration. As a rule, the attacks will not be so severe, but will be manifest to a less degree.

Of the nervous symptoms due to uremia, headache, often of a neuralgic

type, may be the first to appear. Various other disturbances may occur toward the end: changes in manner and temper, dullness, drowsiness, sometimes sleeplessness, and occasionally great restlessness. Speech may be slightly affected and the patient show transient mental failure.

Disorders of vision are quite frequent. In some cases they are due to albuminuric retinitis and to optic neuritis, but in many instances complete amaurosis develops in association with uremic symptoms. In such cases there may be no changes in the fundus of the eye that can be detected with the ophthalmoscope. The sudden onset and transient character of the amaurosis also are hardly compatible with the presence of an organic lesion. Actual blindness may be preceded by a period of dimness of vision or the stage of dimness may be at no time overstepped. Sometimes the patient may emerge from a convulsive attack completely amaurotic, or the blindness may be, for a time at least, an isolated symptom of uremia. The loss of vision may persist for a few hours or less, or for a few days. The pupils usually retain their activity.

Changes in the retinal vessels point not only to probable arteriosclerosis in the cerebral vessels, but are also related to the very early stages of chronic Bright's disease, as has been often urged by many writers. They are highly important from the diagnostic viewpoint, because, as has been insisted on by Gunn, Nettleship, Frost, de Schweinitz, and others, they frequently forerun by a year or two the usual degenerative or toxic retinitis. The ordinary ophthalmologist does not carry his observation quite far enough. Instead of being content with careful inspection of the nerve-head and then sweeping the area of illumination over the out-

lying fundus and into the macular region, he should also inspect* the periphery of the small veins and arteries, and minutely study the vessels at their crossings in every case that is in the least way suspicious. If he finds anything at all suspicious in the vessels, he should see that study is made of the condition of the pulse, the heart sounds, the tracings of the sphygmograph, and the readings of the sphygmanometer. Wendell Reber (Monthly Cyclopedica, April, 1907).

The writer reports 20 cases and concludes that the ocular manifestations of arteriosclerosis are numerous and varied. From the diagnostic standpoint it is the group of signs which occur in the early stages of the disease that are especially important to the general physician. Many patients think themselves in good health and seek the oculist for presbyopic correction in whom a careful ophthalmoscopic examination will reveal the signs, perhaps the very earliest, of beginning arteriosclerosis, and this is the time of all others when something can be done for these patients to avert the more serious later stages of the disease. Bruner (Annals of Ophthalm., Oct., 1909).

The earliest and most common ophthalmoscopic evidences of arteriosclerosis in the retina are irregularities in the caliber of the arteries due to local thickenings of the intima, and constriction of the veins where they are crossed by the rigid arteries. The narrowing of the arterial lumen is sometimes more uniform, and may be such that the blood-columns are reduced to mere threads. To the same stage belong two other conditions, namely, undue tortuosity of the arteries, and an excessive brightness of the central-light streak, giving to the arteries the so-called "silver-wire" appearance. Globular or fusiform dilatations of the arteries, causing the appearance of miliary aneurisms, may also be found. A. T. Ballantyne (Practitioner, Nov., 1909).

Probably among the earliest recognizable signs is the corkscrew appearance of some of the smaller arterial

twigs, notably those in the immediate region of the macula. Or, it may be that one or more of these corkscrew twigs arise from a larger vessel apparently healthy, simply showing that the whole artery is not affected. C. A. Veasey (Jour. of Ophthal. and Otolaryn., May, 1911).

The eye is the organ where arteriosclerosis is often manifested earliest, and where it can most accurately be appreciated by study of the background. Retinitis, especially the degenerative form of albuminuric retinitis, rather than the inflammatory variety indicates arteriosclerosis. The latter is apparently not mentioned among the etiological factors of choroiditis, but it is reasonable to assume that it might be responsible for this, as well as for retinitis. In arteriosclerosis, hemorrhages into the vitreous humor follow rupture of vessels of the retina and choroid. Arteriosclerosis may also prove active in the pathogenesis of glaucoma. Elsworth Smith (Interstate Med. Jour., Jan., 1914).

The *pulmonary symptoms*, other than the uremic asthma, are bronchitis and emphysema, with failure of the right heart. Cases have been reported in which the pulmonary artery has shown very extensive atheroma and sclerosis, with but little involvement of the systemic circulation.

DIAGNOSIS.—A careful consideration of the foregoing discussion will indicate that although there are many symptoms referable to the arteriosclerosis, nevertheless there are many variations from the typical picture. As has been shown; there may be a very extensive alteration in the vessels of some certain portion without equal changes elsewhere. The peripheral vessels may show marked changes without the aorta exhibiting similar conditions, and *vice versa*. Little can be determined from the general appearance of the patient.

He may appear robust and never have complained of sickness, yet his vessels may show extensive disease. Nor can much reliance be placed upon the presence of the *arcus senilis*, as it may be found in middle-aged men with good arteries.

According to Osler, the cardinal points in a case of arteriosclerosis are usually well marked: (1) thickening of the peripheral vessels; (2) signs of hypertrophy of the left ventricle, shown by the apex beat dislocated outward, the thudding first sound, and the accentuated aortic second; (3) heightened blood-pressure; (4) a slight and variable amount of albumin in the urine. As a rule, these symptoms are present in a large proportion of the patients when they first come under observation. Superficial vessels, as a result of the sclerotic changes, may be visibly dilated and tortuous, as in the temples. The brachial arteries may show similar conditions, but if not visible can be recognized by palpation. Care should be taken not to mistake a simple increase in the tension for a thickening of the vessel walls, although the two are commonly associated. In making an examination the vessel should be firmly compressed so as to obliterate the pulse and then felt below the point of pressure. Sometimes it may be well to empty a small section of the vessel and palpation made between the two points of pressure. The left ventricle will usually show signs of hypertrophy, but it may be not always demonstrable to percussion on account of being covered, more or less, by an emphysematous lung. This latter condition is also quite common in the aged, in whom sclerosis is frequently encountered. The pulse is prolonged, hard, and tense, with a

very characteristic sphygmogram. One having a slow, oblique ascent, a broad top, a slow descent, and an absence of the dicrotic rise, which in the normal state depends upon the elasticity that is absent in the diseased vessel.

The pulse tension, taking into account the maximum tension when the body is at rest and comparing it with that during the performance of a certain work, furnishes a measure of the degree of resistance present in the arterial system in arteriosclerosis and of the reserve energy as well as the functional capacity of the heart. Kisch (Med. Klinik, Aug. 8, 1909).

Bulging in the subclavian arteries, where they turn to a right angle to the axis of the aorta, when the walls of the latter have lost their elasticity, is a sign of sclerosis of the aorta. As the aorta cannot stretch, the blood entering it at each pulse wave races with its usual violence into the artery beyond and hits against the upper wall of the subclavian artery at this point. The bulging where it hits this wall can be easily felt with the finger with each pulse wave. Trunccek (Münch. med. Woch., Feb. 10, 1914).

A very important aid in the diagnosis is the blood-pressure; the majority of cases will show a distinct rise. In some instances early in the disease, or before the thickening of the vessels is evident, the blood-pressure may be persistently high. A pressure of over 160 milligrams of mercury can, as a rule, be considered the boundary line between the normal and the abnormal. Up to about 200 mm. of Hg (*vide supra*) one can generally come quite close to a correct estimation of the pressure, but above that point an instrument of precision becomes necessary. It may happen, however, that in many cases of even well-marked arteriosclerosis the blood-pressure is not raised. This may be because the disease is localized to a

part of the arterial tree, or because the heart may at last be giving up the struggle, and hence the pressure, once high, may have fallen. It would seem that localized sclerosis of the splanchnic vessels gives rise more easily to increased arterial pressure than the same amount of disease elsewhere. The increase may also be due to a localized anemic condition of the brain, it having been shown in such instances that the blood-pressure has risen tremendously, evidently an endeavor upon the part of the body to force blood into the anemic area. It must be remembered, however, that in a given case of sclerosis, in which the blood-pressure is found to be raised, it cannot be assumed that the pressure is high because of the disease of the arterial walls, nor yet that the sclerosis is due to the increased pressure. The arterial stiffening may be, for instance, the result of syphilis, and the high blood-pressure to some intercurrent condition of a nervous or toxic nature which may be more or less removable by appropriate treatment.

The new ice test of the writers is a simple and reliable means for ascertaining the functional capacity of the blood-vessels. It consists merely in the application of a piece of ice to the bend of the elbow while the patient is reclining with the arm exposed and the palm up, and all the muscles of the arm relaxed. Every two minutes the pulse is counted for a quarter of a minute, after which the arterial pressure is recorded with a mercury sphygmomanometer. The pulse and arterial tension are thus recorded three times in turn at intervals of two minutes. After an interval of another two minutes the ice is then placed in the bend of the elbow. The pulse and tension are recorded again the moment the ice is applied and again after two, four, and six minutes. After two more minutes the ice is removed, the skin wiped, and the pulse

and tension are recorded again after two, four, and six minutes. The ice must not exert pressure on the arm, which would interfere with the circulation, but must be held. Among 100 persons to whom this test was applied it was easy to distinguish the arteriosclerotics and the tuberculous, as in them the reaction always differed very decidedly from the normal. Under normal conditions in the arterial system the arterial pressure adapts itself to the influence of the ice and there is no modification in the pressure, but the pulse varies, or the pressure may vary and also the pulse, but always according to Marey's law, namely, that the pulse grows slow as the pressure increases and faster as the pressure diminishes. In case of functional incapacity on the part of the vessels the pulse does not vary, but the pressure fluctuates, or both fluctuate contrary to the Marey law. This abnormal reaction occurs frequently in arteriosclerosis, especially with involvement of the aorta. The same abnormal reaction occurs also in tuberculosis, but with the difference that the pressure declines progressively during and after the application of the ice. In arteriosclerosis, the pulse remains stable, while the pressure drops, but the latter rises again as the ice is removed. Among the practical points learned by this test is that arteriosclerotic patients presenting normal curves with the ice test have a more favorable prognosis. Josué and Paillard (*Jour. Amer. Med. Assoc.*, from *Archives des mal. du cœur*, etc., April, 1909).

The writer found that **amyl nitrite** acted differently upon healthy and upon sclerotic arteries, so that it furnishes a means of diagnosing arteriosclerosis with certainty. In healthy persons the preparation causes dilatation of the arteries of the upper half of the body, a slight fall in the diastolic blood-pressure which very quickly returns to normal after the removal of the amyl nitrite because the arteries retain their elasticity. In arteriosclerotic subjects the diastolic blood-pressure behaves differently under the action of amyl nitrite, the fall being very great at first,

and occurring even with increased cardiac action. This would seem to prove that the fall of blood-pressure does not depend upon the heart. K. von Rzentkowski (Merck's Annual Report, vol. xxiii; Merck's Archives, Feb., 1911).

The writer takes his readings by means of two wrist splints of the Mackenzie polygraph, one applied to each radial, and both made to write on a single strip of paper in one of the polygraphs. The apparatus is adjusted so that the best readings are obtained from both wrists and so that they are about equal in oscillation. Then into an arm-let band or a blood-pressure apparatus applied to one arm air is gradually pumped, raising the pressure by 5 to 10 mm. of mercury at a time. When the smallest beats of the pulse in the compressed arm are lost the reading of the pressure in the manometer is taken, and this is considered the minimal systolic pressure. If the pressure is then increased until all of the beats are obstructed, this gives the maximal systolic pressure. It is found that in very irregular hearts there may be a difference of as much as 60 mm. between these two readings. The difference is much less when the rate of the heart is slow than when it is fast. Silberberg (Brit. Med. Jour., April 6, 1912).

ETIOLOGY.—The various causes that can bring about arteriosclerosis may be divided into four classes: the wear and tear of ordinary existence, certain of the acute infectious diseases, intoxications, and those conditions which tend to keep the blood tension high.

It is one of the most frequent of senile changes, but the arteries may in some cases undergo degeneration early in life.

In a series of 2000 autopsies, 442 cases, or 22.1 per cent., showed more or less arteriosclerosis. It is three times as common in the male as in the female, and occurred no earlier in the colored race in this series. The average age of the cardiorenal group was nearly 55.

The average age of the cerebral group was nearly 60. Fifty per cent. of the cases of cerebral hemorrhage occurred in the fifth and sixth decades and was three times as common in the male as in the female. All the cases of aneurism were in males. The average age of death was nearly 45. Death from gangrene and diabetes was incident to the last decades,—the sixth and seventh; the average age nearly 65. W. H. Smith (Boston Med. and Surg. Jour., May 7, 1908).

Case of arteriosclerosis præcox in a man aged 30 who was suffering with rectal cancer. The vascular affection was believed to be due to the toxins of the malignant growth. An atheromatous patch developed in the popliteal artery, and the resulting thrombosis led to fatal gangrene. There was no increased pressure in the case. Klemperer and Benda (Münch. med. Woch., June 20, 1911).

This is particularly evident in those whose occupations involve continuous muscular exertion with consequent increase in the blood-pressure. This condition is of great importance in causing arterial degeneration, and may be due in many to an excess of food and drink. This occasions a constant dilatation of the blood-vessels and also may cause the formation of toxic substances exerting an irritating action upon the arterio-capillary circulation. When food is taken into the body in excess of work and of excretion there is an accumulation of waste.

The writer analyzed the data in 1835 cases of arteriosclerosis and found a history of gout in 323, of rheumatism in 332, of syphilis in 209, of abuse of tobacco in 181, of infectious diseases in 67, of diabetes in 48, of alcohol in 27, of malaria in 14, the menopause in 12, and moral and nervous causes in 19. In 555 cases he was unable to discover any special cause for toxic action. The dyspnea and angina pectoris are due to the kidneys, the angina being the work of the coronaries, while the dyspnea

comes from the kidneys. An exclusive milk diet promptly arrests these phenomena. Huchard (Bull. de l'Acad. de Méd., July 15, 1908).

Small doses of paracresol and indol, acting on the organism over a longer or shorter period, can induce chronic lesions of the nature of sclerosis, the very ones that are most frequently encountered in senility. The phenols and indol found in the stool and urine are not the excreta of our tissues, but are the products of the permanent microbial flora. E. Metchnikoff (Annales de l'Inst. Pasteur, Oct., 1910).

The causes of arteriosclerosis may be summed up under the heads: (1) toxic —e.g., lead, infections of all sorts, excess of certain internal secretions, such as adrenalin, and absorption from the intestinal tract of certain putrefactive products; (2) senile or quasisenile, in which would be included the wear and tear from overwork, and (3) heredity. J. M. Jackson (Boston Med. and Surg. Jour., Nov. 4, 1911).

Certain toxins of extrinsic origin will bring about marked changes and the two probably most important are alcohol and lead; tobacco may also be included. The great difficulty in ascribing arteriosclerosis to any of these conditions is due to the impossibility of determining which of several factors may have been the most important element. There is, however, a widespread doubt concerning the effect of alcohol, there being many who do not believe that its indulgence tends to cause sclerosis. If it does exert any effect it may be by acting as a direct poison, causing necrosis of certain elements of the blood-vessels, or it may be concerned in bringing about a constant high blood-pressure.

Only 6 per cent. of 283 cases of chronic and excessive alcoholism under 50 years of age, examined by Cabot, showed any evidence of arteriosclerosis. Of 45 cases of this affection examined by the author at the Massachusetts General Hospital,

only 13 per cent. gave any history of alcoholism. Of 656 autopsy cases of arteriosclerosis, only 95, or 14.5 per cent., were under the age of 50. Out of these 95 cases under 50, in which arteriosclerosis was found *post mortem*, only 21 per cent., and if the cases complicated by chronic nephritis are excluded only 17 per cent., appear to have consumed alcohol in any notable excess.

Tobacco may exert an influence inasmuch as extensive degenerative changes may be brought about experimentally in the aorta. It increases the tension and may give rise to spasmodic contractions of vessels.

Lead poisoning may give rise to renal disease and arterial changes. It has long been known that lead is an important factor in the production of gout, and it is probable that both lead and the toxic agents of gout cause defective metabolism. As both gout and chronic interstitial nephritis are associated with increased blood-pressure we have conditions present that are favorable to sclerosis. It may be that the thickening of the arteries in gout, in diabetes, in chronic Bright's disease, and in obesity may be due to the action of retained poisons upon the blood-vessels.

According to Billings lead may produce arteriosclerosis either directly or indirectly. Directly, as shown by the numerous experiments on animals. Probably this is by the direct influence on the vessel of the lead in the circulating blood. Doubtless the walls of some of the larger arteries may be affected through the alteration in the nutrition because of the primary toxic endarteritis, with the tendency to thrombosis and obliteration of the vasa vasorum. The undisputed fact that lead may cause gout, and the equally true proposition that in gouty individuals arteriosclerosis occurs early, may explain the influence of lead in producing arteriosclerosis in rare cases. Experimental and clinical observations prove incontestably

that lead will cause nephritis. This is usually the contracted kidney, which sooner or later has associated with it the thickened arteries and left cardiac hypertrophy. Lead intoxication may lead directly and indirectly to arteriosclerosis. The recognition of lead intoxication during life, by any of the ordinary symptoms or by the basophilic granulations of the cells of the blood, in an individual suffering with arteriosclerosis, with or without nephritis, would not, perhaps, permit us to say definitely that the lead was the sole causative disease factor. It would, however, be a rational therapeutic measure to safeguard the individual against further intoxication with lead in the treatment of the arteriosclerosis.

Although various infective diseases, such as scarlet fever, measles, small-pox, diphtheria, and typhoid fever may give rise to arterial changes, none is probably more productive of arterial degeneration than syphilis. It may bring about an endarteritis of the vaso vasorum and a defective nutrition of the walls of the arteries; or by the devitalizing influence of a toxin, long present in the body, produce anemia and a lowering of the physiological margin of normal metabolism. Consequently, in case of injury or stress of a tissue, the equilibrium is not maintained and degeneration ensues. Syphilitic arteritis may affect simultaneously or successively a number of arteries, and in some instances it gives rise to a general affection of the small arteries and arterioles. It may be limited to the aorta or even to the coronary arteries, but the most frequent and important site of the disease is the brain. Particularly those vessels which enter into the formation of the circle of Willis (the vertebrals, and the basilar together with the carotids) and its branches.

In addition to the above causes, scle-

rotic changes may appear in the ordinary course of existence as part and parcel of the constant wear and tear. To quote from Osler: "Among organs the blood-vessels alone enjoy no rest. Not only does a ceaseless rush of fluid pass through them at a speed of 10 inches a second, but the walls of the main pipe are subjected to a distending force of $2\frac{1}{5}$ pounds to the square inch, 60 to 80 times a minute, 80,000 to 100,000 times in twenty-four hours. The heart has rest in diastole, but, distended by the charge from the left ventricle, the arteries pass it on partly by the natural elasticity of the walls, partly by an active contraction of the muscle fibers. Like other organs they live under three great laws: use maintains and in a measure sustains structures; overuse leads to degeneration; in time they grow old, in three score or four score years the limit of endurance is reached and they wear out. The stability of tubing of any sort depends upon the structure and the sort of material used; and so it is with the human tubing. With a poor variety of elastic and muscular fibers in the blood-vessels, some are unable to resist the wear and tear of every-day life, and have at 40 years of age arteries as old as those of others at 60. They look the same macroscopically and microscopically, but they differ in different individuals in the quality of the materials used and the capacity to resist the ordinary stress of life. In the fourth or fifth decade, even with the best of habits in eating and drinking, the incessant strain and anxiety of public life or business may lead to degeneration of the blood-vessels. Mental exertion is not of itself injurious, and the life of the student need not be

one of great tension, but the mental exertion of the modern business man is of a different kind. Competition is so keen and the environment so stimulating that even without political or social ambitions high pressure seems a necessity."

After 40 it is exceptional to examine the arteries without finding evidence of degeneration—here and there a small plaque of atheroma, an occasional streak of intimal fatty degeneration, and with this the mitral and aortic cusps may have lost just a little of their delicateness. With advancing age the arteries become thicker and the atheromatous changes more marked. As a rule, in the very aged not only the smaller arteries are thickened, but the aorta and its main branches show extensive changes with calcification. Living quieter lives and with less strain and stress, women are not so frequently the subjects of arterial change and consequently they last longer. In infants and young children arteriosclerosis occurs: 1. As occasional patches or flakes, or even calcified foci, in the vessels of the newborn. 2. In infants dying of the acute infections, streaks of fatty degeneration of the intima and foci of necrosis of the media are not uncommon. 3. Widespread arteriosclerosis of the smaller vessels may occur without nephritis and without recognizable cause. Two or three cases may occur in the same family. 4. In congenital syphilis, diffuse or localized sclerosis of the arteries may occur, sometimes early, sometimes as a late manifestation in latent hereditary syphilis.

According to Thayer typhoid fever plays some causal part in the thickening of the radial arteries. An analysis of the histories of 3894 cases in Dr. Osler's wards showed that no causal factor existed

in a percentage of 18.9, and in cases of diphtheria a slightly lower percentage, then pneumonia with 19.6, malaria 22.6, syphilis 23, scarlet fever with 24, diphtheria with 28.7, rheumatism 41, alcoholism 53.3, and heavy work 62.2. So far, the writer is not justified in drawing any conclusions that acute infectious diseases played a part in the development of arteriosclerosis.

Arterial disease seems to be attributable to syphilis, according to Camac, in about 32 per cent.; to tuberculosis in about 16 per cent. The facts presented go to show that the colored race is affected about four times more frequently than the white. General arteriosclerosis seems to be not commonly found with aneurism, and its presence may be considered as evidence against the probable development of aneurism.

A history of syphilis was found in 28 of 37 cases of aortic insufficiency; in 4 of 5 cases of bradycardia; in 6 of 6 cases of aneurism, and in 2 of 3 patients with constant arrhythmia, all due to arteriosclerosis. Even with organic angina pectoris in persons under the age of 50, the writer found 6 syphilitics in 11 cases; above this age only 3 in 41 cases. In a total of 92 patients with heart disease of the sclerotic types syphilis was admitted by 54 of the patients; a positive Wassermann reaction establishes the diagnosis in many cases. One of the patients had had permanent slow pulse for forty-seven years after the primary sore, and gave a marked Wassermann reaction. Specific treatment generally comes too late to do much good, although the pains may be relieved. Fiessinger (*Bull. de l'Acad. de Méd.*, Oct. 10, 1911).

Anaphylaxis due to food proteins has recently been adduced as a causative factor, the subject becoming sensitive to special agents of this class present in certain articles of diet, particularly meats and eggs.

Arteriosclerosis is not the effect of proteins on the individual but the reaction of the individual to the proteins. The vegetable proteins apparently cause the least harm. The disease is liable to begin when, through

some accident of food poisoning, severe illness, nervous shock, or some unknown incident, the cells of the body become sensitive to particular proteins found in customary food. Later there is a continuous subsymptomatic anaphylaxis, leading to irritation and finally to changes in the tissues—perhaps to replacement of some of the cells by connective tissue. This takes place in all parts of the body. The impairment of the organs leads to failure of the internal secretions and of general metabolism, and the individual, who started with a sensitiveness to a single protein is found, after perhaps 25 years, to present the picture of the terminal stages of so-called Bright's disease. L. F. Bishop (*N. Y. Med. Jour.*, Sept. 13, 1913).

In a study of the arterial lesions produced by feeding egg yolk and cholesterol or cholesterol fat to rabbits, the writer confirms the findings reported by others. After a period varying from 30 to 348 days, 11 of the 15 animals showed in both the aorta and pulmonary artery small raised yellowish white spots and streaks close under the inner lining. The spots contained large cells with fat containing droplets which were anisotropic, associated with proliferation of fibroblasts and fine elastic fibers. Fatty degeneration appeared in the media occasionally. The adrenal was not infrequently found much enlarged. It is probable that the adrenal has some function in the storage and metabolism of the cholesterol. Bailey (*Jour. Exper. Med.*, xxiii, p. 69, 1916).

The ductless glands have been advanced by Sajous as pathogenic factors. This feature of the problem is treated under the next heading.

PATHOLOGY.—The nature of the arteriosclerotic process has been very thoroughly gone into by Adami a few years ago. According to his description, in the aorta and its larger branches, those which contain elastic tissue, the following main types may be found:—

1. The ordinary nodular arteriosclerosis. This manifests itself in the beginning as a thickening and overgrowth of connective tissue, especially at or around the openings of the small branches, as yellowish-white thickenings, notably affecting the origins of the series of intercostal vessels. Later these may grow in size, and sometimes coalesce, forming in the aorta projecting flattened nodes. These may be scattered somewhat irregularly through the aorta, becoming more abundant and more advanced in the abdominal region. It is this form that more especially goes on to atheroma and calcification of the intimal plaques.

From a careful histological study of the changes found in the radial artery the writers conclude that, whereas in old age a thickened radial artery is normal, an unduly thickened radial artery at an earlier age may mean one of two things: that the vessel has been subjected to unusual or exceptional strain, or that the vessel, from inherent weakness or other abnormality, has been unable to cope with conditions which might ordinarily be regarded as normal. The artery has thus been obliged to fortify itself by progressive thickening of its walls. As a rule, although there are striking exceptions, when the thickening of a radial artery is unduly marked, similar changes occur in the mesenteric artery and aorta. W. S. Thayer and M. Fabry (*Amer. Jour. Med. Sci.*, Dec., 1907).

So-called calcified arteries are not of a stony rigidity during life, the calcareous matter in the arterial wall being soft—a state that may be compared with unset mortar. In arteries provided with an adequate circulation the calcareous matter, whether it be in the intima or the media, remains unset. This tends to explain why, after handling pipe-stem radials, there is no thrombosis and gangrene, and also why rigid and tortuous splenic and other mesenteric arteries in the

aged arteriosclerotic do not undergo traumatic rupture. A. H. MacCor-dick (Brit. Med. Jour., Oct. 18, 1913).

2. In this form the radials may be distinctly hardened and even calcified, yet an examination of the aorta may disclose the complete absence of nodose thickenings of the intima. In the thoracic portion especially there may be a diffuse dilatation of the aorta. Instead of being thickened, the aortic wall appears to be thinned and there is evidently an increase in the length as well as in the breadth of the vessel. This is indicated by the aorta running a somewhat tortuous course. In the aorta and the common iliacs there are found slight transverse depressions. This latter condition is evidently a degeneration, but not a sclerosis. It will be found, however, that in these cases the smaller arteries are markedly sclerotic, with localized areas of intimal fibrosis, with hypertrophy and fibrosis of the middle coat, and often with well-pronounced periarterial fibrosis. The hardening of the radial and the other middle-sized arteries is not, as a rule, dependent upon an increase in the amount of connective tissue, but to a calcification of the media. This may have been preceded by a marked hypertrophy of the muscular coat.

A study by Ophuls of 75 cases varying from the early appearance of a few scattered, slightly prominent, yellow, translucent spots in the intima to the severest lesions presenting loss of elasticity and dilatation showed that it is impossible to subdivide the condition anatomically into separate groups, as the disease is a chronic inflammatory process which attacks all the coats of the aorta simultaneously, the lesions being sometimes more marked in the intima and sometimes more in the media and adventitia, but generally the intima and adventitia are the first to show noticeable changes. In the former, pro-

liferation of the connective-tissue cells takes place, followed by a fibrous thickening, and in the latter cellular infiltration occurs around the vasa vasorum, ultimately leading to a fibrous thickening of the external coat. In the muscle little may be found beyond a slight collection of cells around the vasa vasorum.

The dominant primary event in the arteriosclerotic process—syphilitic, senile, or functional—is a localized or it may be a diffuse weakening of the arterial wall, and especially of the media. This induces strain on the remaining coats; and if this be not excessive, the changes caused by that strain lead more especially to connective-tissue overgrowth and to the development of the characteristic lesions of arteriosclerosis. J. G. Adami (Amer. Jour. Med. Sci., Oct., 1909).

The toxic agents, either chemical or bacterial, may come either through the blood stream in the lumen of the artery or through the vasa vasorum, the latter being the principal medium, especially for bacterial factors. Thus, most bacteriologic degenerative changes originate as a mesarteritis rather than as an endarteritis. Syphilis is the most frequent of any of the factors which are definitely known to be in themselves solely responsible for arterial degeneration. B. A. Shepard (Mich. State Med. Soc.; Jour. Amer. Med. Assoc., Sept. 9, 1916).

A number of observers have noted the spontaneous development of canine arteriosclerosis. Koellisch found vascular sclerosis in 10 out of 50 working dogs and 13 out of 50 pet dogs. This would suggest that the hard work imposed upon dogs on the continent has no influence in bringing about sclerosis of the arteries. Strauch (Ziegler's Beit., lxi, p. 532, 1916).

In a study of 500 persons to ascertain whether infectious diseases played an important part in the production of arteriosclerosis, the writer was led to conclude that they play little or no part in its etiology. Warfield (Jour. of Lab. and Clin. Med., Nov., 1917).

3. This type is the syphilitic, in which the aortic manifestations are quite similar to the ordinary nodose arteriosclerosis. It can, however, be distinguished generally from the latter both macroscopically and microscopically. The usual location is the ascending aorta and the arch, where the nodes are found in groups. They are comparatively large, semitranslucent or hyaline in appearance. Atheromatous and calcareous changes are not common, and in the later stages there occurs a scarring with a central depression. Microscopic examination shows that the primary lesion is a subacute meso-arteritis, with an infiltration of small round cells about the branches of the vaso vasorum and absorption of the elements of the media. This involves both the muscular- and elastic-tissue layers, the absorption of the latter being very striking. This is the primary change. The process does not extend beyond the media into the intima, but, as a secondary process, the intima undergoes a proliferative thickening. When the deeper portions undergo necrosis the underlying granulation tissue projects new capillaries into the degenerated area. The necrotic material becomes absorbed, is replaced by connective tissue with subsequent scar formation and contraction.

In the radials and vessels of similar size, a form of change frequently called Moenckeberg's sclerosis is common. In this type there is a widespread degeneration of the media with calcification, the intima being also much thickened. His conclusion is that medial calcification is more frequent in the peripheral vessels than thickening of the intima alone. The senile arteriosclerosis commonly shows this medial

degeneration, and it is found that the "pipe-stem" radial, for example, is a condition of medial and not of intimal calcification.

In the smaller arteries and arterioles there is great variation in the appearance in different cases. These differences probably represent different stages of the same process, modified possibly by variations in the reactive power of the tissues, intimal and medial. Two broad groups may be recognized: (1) that in which pronounced thickening and hypertrophy of the muscularis are the most marked features, and (2) that in which a generalized proliferation of the intima predominates. The first probably represents the earlier condition. The first effect of the substances in the blood is to stimulate the smaller arteries to increased contraction, and in this way bring about an hypertrophy of the muscle-cells. It is to this generalized contraction of the smaller arteries and arterioles that must be ascribed the continued elevation of the blood-pressure. Eventually the muscle-fibers degenerate and fail to maintain the narrowed lumen. Where there is a progressive process, and the artery as a whole tends to give way under the internal pressure, there is developed a compensatory fibrosis and thickening of the intima, with simultaneous evidence of atrophy and fibrosis of the media. Frequently associated with these changes in the arterioles is a surrounding fibrosis, a chronic periarteritis. When the capillaries are involved in a widespread process, the arteriocapillary fibrosis of Gull and Sutton results.

In the larger vessels, as the aorta, the earliest change is the appearance of small streaks in the intima; opaque, white, fatty looking, and tending in

general to a longitudinal arrangement. They are most common in those dying from infection and acute intoxication. Microscopic examination shows that they are not, as usually considered, confined to the endothelium, but represent a fatty degeneration of the deepest layer of the intima, the musculoelastic. In addition to these, certain bacteria and their toxins lead to a definite proliferation of the aortic endothelium and intima—a true proliferative intimitis. It is somewhat doubtful whether this should be regarded as a true arteriosclerosis, as evidence is lacking that this intimal thickening proceeds onward to the familiar picture of the atheromatous aorta. The typical arteriosclerotic aorta shows changes which to the naked eye characteristically affect the intima. That undergoes a notable thickening, not uniform but nodose, although in advanced cases the thickened plaques may be so close that they fuse into large areas. In these plaques there occur a succession of stages. The slightest cases are those in which there is a proliferation of the superficial layers of the intima, forming a layer of dense fibrous tissue, the fibers running parallel to the surface. In another form there may be a somewhat similar proliferation of the deeper, musculoelastic layer of the intima, not so purely fibrous, but exhibiting also a proliferation of yellow elastic tissue. In either case there is present a simple hyperplasia of the intima, with no sign of leucocytic infiltration, of new vessel formation, or of inflammation as usually accepted. Degenerative changes in the plaques are more frequently encountered. The layers nearest to the intimal surface may show little or no change, but deeper down (1) the layers

become swollen and hyaline, or (2) as a more advanced change exhibit fatty degeneration, loss of nuclear staining, disintegration of the tissue, with the presence of cholesterin plates. There is also evidence of necrosis and autolysis. These are the typical atheromatous lesions. When suitably stained such softened areas show the presence of calcareous matter. This may accumulate, becoming more and more abundant, until gritty masses and extensive brittle plates of calcification become developed. In either of these latter stages the superficial, thin, but hitherto intact layer of the intima may give way and be torn off, an *atheromatous ulcer* being formed, shallow, and with a rough, necrotic floor. Before the breaking down of the intima the areas of softened semifluid substance are sometimes spoken of as *atheromatous cysts*. As the intima normally possesses no blood-vessels, it happens that with the progressive laying down of layers of dense fibrous tissue the nourishment of the older, deeper layers becomes cut off and necrosis results. Except in syphilis it is unusual to find a secondary granulation process occurring in the atheromatous plaques with the entry of capillary loops from the vaso vasorum of the media. When this is the case there is found a distinct reparative process, absorption of the atheromatous material, and a laying down of new fibrous tissue to replace that which has undergone necrosis. Where this is the case the plaques, instead of remaining flattened, become puckered, often with an obscurely stellated depression. This puckering is the main naked-eye indication of syphilitic aortitis.

Concerning aortic arteriosclerosis the following appear to be the facts so far

determined: 1. That a weakness and giving way of the media constitute the primary anatomical lesion in the great majority of cases. 2. It is possible that, as the result of a subacute proliferative intimitis due to bacteria and their toxins, the thickening of the intima, by cutting off the nutrition of the inner layers of the media, may weaken that coat and so cause a local dilatation of the lumen of the aorta; this, in turn, followed by a secondary and further thickening of the intima. But it is also possible that the infective endarteritis which undoubtedly exists has no direct association with the general process here described. So that when after typhoid and other infections there develops a premature arteriosclerosis, the condition is one of a primary sporadic degeneration of the media set up by the bacterial toxins. 3. The affection of the media may be either a primary degeneration without signs of preceding inflammation or may be of inflammatory origin, as in syphilis. 4. The intimal change secondary to medial degeneration has none of the features of an extension of the morbid process from the media, but is of a wholly different nature. It is primarily of hyperplastic type—a senile connective-tissue hyperplasia unaccompanied by the phenomena which we associate with inflammation.

In order to understand the meaning of the various changes occurring in arteriosclerosis much experimental work has been done on the lower animals. In 1889 and also in 1904 Gilbert and Lion produced changes in the media by repeated intravenous injections of micro-organisms, paracolon and typhoid, or their toxins.

Changes observed in the peripheral vessels of young people, and even chil-

dren and infants dying from various acute infectious diseases. All parts of the peripheral arterial vascular system were examined. Eighty cases of diphtheria were studied, 80 of scarlet fever, and many cases of other infectious diseases. In every instance the writer found a disease of the peripheral vessels that manifests itself as a degeneration of the smooth musculature and of the elastic fibers, which is to be seen first in the middle coat and in the majority of cases is confined to this one tunic. The degeneration appears in localized areas which in certain vessels may be very numerous, and in severe cases leads to a veritable necrosis of the vessel wall. These necroses heal either through scarring or by *restitutio ad integrum*. In many cases, however, the process extends into the intima, in which case this coat undergoes sclerotic changes whereby permanent injury is produced. Though these changes are usually of microscopic nature, in extreme cases they may be visible to the naked eye. The disease affects all arterial vessels down to those of the caliber of the digital arteries. Wiesel (Zeit. f. Heilkunde, Bd. xxvii, S. 262, 1906).

The writer found lesions of arteriosclerosis in the aorta after repeated injections of filtrates or emulsions of cultures of staphylococci in rabbits and monkeys. Manouelian (Jour. Amer. Med. Assoc.; Annales de l'Inst. Pasteur, Jan., 1913).

In a series of investigations on the nature and cause of the arterial degeneration the writer ascertained that out of 6 cases of streptococcus septicemia the organism was isolated 4 times from the aortic wall, the staphylococcus twice out of 3 cases of septicemia. In 7 cases of malignant endocarditis, however, the organism was not found in the arterial tissues. Similar negative findings were obtained in pneumonia. On the other hand, a positive result was once obtained out of 5 cases of acute rheumatic fever. Associated with *B. coli* infection the aorta was invaded by this organism in 4 out of 5 cases. F. W. Andrewes (Ann. Rep.

of Local Government Board, Appendix B, p. 151, 1913-14).

The writer studied the occurrence of hyaline in various portions of the arterial coat. Its first appearance is in the spleen and ovaries; here it may be found after the age of fifteen years. In other cases it followed acute infective diseases. In the kidney it appeared more frequently about the capillaries of the glomeruli following various grades of renal inflammation. In the later stages of the kidney affection the larger arteries also show hyaline degeneration occupying the middle coat of their walls. In the large arteries hyaline appears with greater frequency with advancing age and here it is to be looked upon as the evidence of many insults brought to bear upon the arterial coats. Under some conditions the hyaline deposit represents a process of degeneration secondary to a tissue reaction of a proliferative kind. This is particularly true of the hyaline in the nodular thickenings of the intima of the aorta. On the other hand the development of band-like deposits of hyaline in the deep portions of the intima suggests a tissue response resulting from a systemic process. Jacob (*Jour. Med. Research*, xxxv, p. 187, 1916).

As an increase in blood-pressure was considered an essential factor, experiments with epinephrin were undertaken with the production by Josué of lesions similar to those in the human being. The action of the epinephrin is directly exerted upon the muscle of the smaller arteries and causes this to contract. The effect is temporary, but if the injections be repeated in the rabbit there is developed, eventually, a profound alteration in the aorta. Sajous attributes this to constriction of vasa vasorum and the resulting denutrition.

There is apparently an analogy between the condition described in the rabbit after intravenous adrenalin injection and the calcification of the

media as found in the large arteries of the extremities in man. The writer believes that this vascular disturbance is not due to an increase in blood-pressure or to nutritive changes brought about by spasm of the vasa vasorum, but is due rather to a direct toxic effect of the adrenalin on the smooth muscle-cells of the vessel wall. Erb (*Archiv f. exper. Pathol. u. Pharmak.*, Bd. liii, 1906).

The writer concludes that adrenalin produces vascular lesions similar to those of arteriosclerosis by causing excessive constriction of the arterioles from which the vasa vasorum receive their arterial blood. The vascular tissues to which these minute vessels are distributed being inadequately nourished, they finally become necrotic and are converted into atheromatous or sclerotic patches. Councilman found the degeneration in the media and adventitia chiefly about the vasa vasorum. Cowan noted the same lesions in the aorta. Sajous ("*Intern. Secretions*," vol. ii, p. 1556, 1907).

Sajous adopts, in modified form, the theory of hypertension. He holds that arteriosclerosis is primarily due to the presence of endogenous or exogenous poisons in the blood, but does not believe that these poisons act directly upon the vascular walls. They stimulate the adrenals to destroy the said poisons, but this surplusage of adrenal secretion expends its action upon the cells of the vascular walls, and is most disastrous in the minute vasa vasorum, the lumina of which become obliterated. In consequence, the large vessels are imperfectly nourished and undergo sclerotic and calcareous changes.

It seems evident from the above that, in the opinion of Sajous, the secretion of the adrenals does not produce arteriosclerosis solely through the hypertension which it induces, but that its action may also be fairly styled toxic. This view is confirmed by the very recent researches of Waterman which were published in the last February number of Virchow's *Archiv*. As the result of his experiments and pathological studies, Waterman concludes that adrenalin produces arteriosclerosis

rather through its toxic influence than through its elevation of blood-pressure. F. P. Henry (*Monthly Cyclopedica and Med. Bull.*, June, 1908).

The changes that develop do not correspond accurately with those of the ordinary nodose sclerosis, but they are, however, indistinguishable from the changes seen in Moenckeburg's type of medial degeneration. There is the same atrophy of the muscle-fibers and giving way of the media, with the production of pouchings which at times are so extreme as to become definite, small, sacular aneurisms. There is a fatty followed by a calcareous degeneration of the muscular layers, with secondarily a similar calcareous degeneration of the elastic-tissue elements of the coat.

Injections of adrenalin into the blood-vessels of rabbits produced changes which have nothing in common with arteriosclerosis. The writer believes they bear some resemblances to syphilitic sclerosis of the arteries and to neurotic angiosclerosis. The origin of the changes seems to lie in the median coat of the arteries. Lissauer (*Berl. klin. Woch.*, May 22, 1905).

The writer varied Josué's experiments in producing arteriosclerosis in rabbits by intravenous injections of adrenalin, in that he had injected amyl nitrite at the same time and yet the arterial sclerosis had followed. This showed that its production was not due to the action of adrenalin in raising the blood-pressure, but to its action as a poison. Ludwig Braun (*Wiener klin. Woch.*, Nu. 6, 1905).

Among these arterial poisons, adrenal extracts, lead, tobacco, ergot, and theocin have a decidedly elective action on the arterial system, in which they induce calcification. The aorta suffers most, and rabbits and cows are affected more than dogs, possibly owing to their vegetable diet. The calcification is due more to a nutritional disturbance than to inflammation or necrosis. Loeper (*Presse méd.*, vol. xiv, No. 29, 1906).

Experiments on 61 rabbits to which varying doses, from 0.5 m. to 15 m. (0.03 c.c. to 0.9 c.c.) adrenalin chloride, 1:10,000, were given hypodermically three times a day for periods varying from one to forty or more days. There was no constant relation apparent between the extent and frequency of the lesions found and the size and frequency of the dose or the duration of the treatment. The extensive lesions were found in a rabbit that had received only 150 m. (9 c.c.) altogether in 5-m. (0.3 c.c.) doses, while others receiving from four to eight times as much showed no lesions whatever. Arterial lesions were found in 17 rabbits out of the 61, a percentage of 27.86. Similar tests were made on 49 assumedly normal rabbits with like results, lesions being found in 17 out of the 49, or in a percentage of 34.77. A. M. Miles (*Jour. Amer. Med. Assoc.*, Oct. 5, 1907).

The writer examined 62 rabbits to ascertain the occurrence of spontaneous arterial degeneration noted by Miles and Johnstone. These lesions do not, in his opinion, diminish the importance of the lesions due to adrenalin, but rather increase it, as an example of a lesion occasionally occurring naturally, but which may be readily produced experimentally. It in no way vitiates the importance of the experimental lesions, but does demand a very careful control study of the rabbits in each locality in which experiments are made. R. M. Pearce (*Jour. Amer. Med. Assoc.*, Sept. 26, 1908).

More or less similar results have been obtained by the intravenous injection of digalen, nicotine, phloridzin, and various synthetic products resembling epinephrin, and the administration of lead salts and tobacco by the mouth.

Arteriosclerosis is due to the presence in the blood of deleterious substances of varying nature: some increase the arterial tone by stimulating the unstriated muscle-fiber directly or indirectly through the nervous mechanism, while others have a depressor

action. As an evidence of the presence of such bodies the author has found the freezing point of the blood lowered in all well-marked cases of arteriosclerosis. Long-continued straining of the arterial coats impairs the elasticity and nutrition of the vessels, and leads to chronic inflammation of the intima, with subendothelial cellular hyperplasia. This cell proliferation appears as white patches, which break down, leading to ulceration and aneurism, or lime salts are deposited, leading to calcification. The arch of the aorta suffers most in this process. In smaller arteries, not subject to strain, there is hypertrophy of the muscular coat and subendothelial hyperplasia. It may be that there is an excess of adrenalin secreted in this case. Barr (Brit. Med. Jour., Jan. 14, 1905).

The numerous deaths from influenza in 1918 facilitated post-mortem study of the arterial system in robust young people. In a study of sclerosis of the coronary arteries the writer found evidence of it or of fatty degeneration in only 23 per cent. between the ages of 18 and 20; from 21 to 30 the proportion was about the same as that observed in Germany, viz., about 46 per cent. in men and 17 per cent. in women. It has been said that in Germany no coronaries are ever found intact after 40, but at Geneva he found 12.8 per cent. intact in the fifties and 20 per cent. in the sixties. Orliansky (Revue Méd. de la Suisse Rom., June, 1919).

The participation of the ductless glands in the morbid process have been further emphasized by Sajous in the sense that the adrenals are not regarded as acting alone in the morbid process, but in conjunction with the thyroid.

The writer divides the disease into three types:—

1. The *adrenal type*, due to over-activity of the adrenals (and, through their hormone, of the thyroid gland also) observed in persons subjected to hard physical exertion, blacksmiths, letter carriers, hod-carriers,

bicyclists, etc., with high blood-pressure, exuberance, pains in the calves of the legs, slow full pulse, hard systolic cardiac impulse, "palpitations," muscular pains, hyperchlorhydria, pyrosis, as more or less clearly defined symptomatology in which the vascular walls are thickened, hyperemic, but not necessarily the seat of degenerative lesions, unless excessive constriction of the vasa vasorum have so reduced the nutrition of certain areas as to cause them.

2. The *autolytic type*, where slowly acting poisons, food proteins, over-feeding, alcohol, the excessive use of coffee, etc., with exaggerated metabolism and focal autolysis in the vascular walls due to the presence in the blood of an excess of antibodies evoked therein by the poisons, or by some acute febrile (bacterial) disease. In the overfed we may witness as early symptoms those enumerated above, with flushed face, brilliant eyes, slight precordial pain after a copious meal or exertion, sometimes slight, and general vivacity. This stage in reality corresponds with the active period of an infection which, though relatively short, may do considerable damage to the blood-vessels. The patient then passes into what is erroneously described in some text-books as an early manifestation of first stage, but which in reality is a more or less advanced phase of the disease, in which the contractile power of certain areas of the arterial system are already compromised. When this stage is reached the syndrome recalling neurasthenia develops more or less clearly, i.e., those of a debilitated and unevenly distributed circulation: loss of vigor, lassitude or myasthenia, drowsiness, postural vertigo, faintness, more or less visual disturbances—hemianopsia or even amaurosis—phobias, headache, and dyspnea on exertion.

3. The *denutrition type*, in which in addition to the arterial lesions there is exhaustion of the adrenals and thyroid through the excessive functional activity imposed upon them by the

pathogenic toxic, whatever that may be, the patient having then reached what has been termed the "presenile stage" of arteriosclerosis. In some subjects this may develop early, even in those of frugal habit, because their ductless glands, including the thymus, through inherited debility, are unable to bear the least exacerbation of activity, physical, mental and also emotional. In others, again, the ductless glands may have become debilitated through local hemorrhages with resulting functionless areas, as a result of febrile infections of childhood, diphtheria especially. Such cases of denutrition arteriosclerosis are often the prey of tuberculosis and pneumonia. They grow old early because as the wear and tear of life impinges upon their ductless glands, denutrition progresses, including that of the arterial system. C. E. de M. Sajous (*N. Y. Med. Jour.*, May 26, 1917).

Many theories have been advanced as to the direct cause of the process, such as high tension, toxic influence, spasm of the vaso vasorum, and cachexia. Of these the toxic and high tension have the strongest support at the present time. There is considerable evidence that extracts of the adrenal have a toxic action quite independent of their vasomotor effect, but the arterial changes do not seem to appear unless there has been accompanying increase in blood-pressure. Harvey employed temporary digital compression of the abdominal aorta of a rabbit on many successive days. Klotz took healthy, young rabbits and suspended them head downward for three minutes daily for one hundred and twenty days or more. In both cases the only disturbance produced was a rise of blood-pressure in the thoracic aorta and its branches. No drug was introduced, but the changes were of the same type as those obtained by epinephrin. In Klotz's experiments

the heart was found distinctly hypertrophic; the thoracic aorta showed a diffuse, almost aneurismal dilatation compared with the abdominal aorta. There was little sign of intimal sclerosis, but section showed well-marked medial degeneration of the Moenckeburg type. The main vessels of the neck exhibited most typically a sporadic intimal sclerosis of the nodose type, indistinguishable from the condition as seen in man.

It would seem, as a result of the many investigations, that raised blood-pressure may induce (1) a localized giving way of the media, or (2) a diffuse giving way of the same with no accompanying overgrowth; in the first place causing a saccular, in the second a diffuse fusiform aneurism; or (3) it may cause a slighter degeneration and giving way of the media, which now is accompanied by pronounced proliferation of the intima. These contradictory conditions are explained as follows by Adami under the terms of "strain hypertrophy" and "overstrain atrophy." It is well known that, provided the nutrition be adequate, muscle-fibers, whether striated or plain, when subjected to strain slightly above the normal, undergo both hypertrophy and hyperplasia; such moderate work is a stimulus to increased growth. Subjected to greater strain, they, on the contrary, become exhausted and tend to atrophy. This same law holds good generally. If the media gives way only slightly and gradually at the region where it bulges, the overlying endothelium and intima, being pressed outward, become stretched as a result of the increased strain. As long as this strain is not excessive the cells proceed to multiply until the concavity is filled up

and the strain removed. The explanation of the difference in the results of the experiments between the aorta and the carotids is that the artery with the smaller lumen and relatively more powerful media can stand a greater dilating force than the artery of larger lumen and relatively weaker walls. The sclerotic thickening of the intima, therefore, is in no sense an inflammatory process any more than is cardiac hypertrophy. At the most it is compensatory to the weakening of the media. On the other hand, when the giving way of the media is more extreme and more rapid in its progress, there the strain to which the intima and endothelium are subjected becomes excessive, and proliferation of the cells is inhibited, so that aneurism formation takes the place of compensatory fibrosis or sclerosis.

TREATMENT.—As in most diseases so in arteriosclerosis, prevention is the chief aim. If there have already occurred fibrosis, degeneration, and calcification there is little to be done, as nothing can restore the vessels to their normal condition. Since arterial hypertension is an important precursor of arterial degeneration, any course of treatment that will prevent the former will consequently ward off the latter.

As the high blood-pressure is essentially no more than a vascular reaction against the presence of toxins in the circulating blood, the primary indication is to get rid of these irritating substances. This can be accomplished by regulating the diet and general hygiene, paying special attention to the secretory organs. The control of the diet does not imply merely a cutting down of the amount of meat, although it is well recognized that an excess of meat pro-

teins is unquestionably harmful. Other foods should also be restricted; an excess of either carbonaceous or protein food elements is hurtful. It has been noted, however, that less toxemia will result and less work be required of the organism to obtain its proportion of nitrogen from flesh than from vegetable proteins. If the kidneys are not involved meat may be allowed, particularly at the midday meal, the amount being strictly limited to the actual needs of the individual. The chief thing is moderation along all lines. In the case of corpulent patients there should be some decrease in weight, while, in the thin, care should be taken that they either do not lose or rather that they should tend to increase in weight. What should be sedulously avoided is a combination of freedom in indulgence of food and lack of physical exercise. This can readily cause a marked rise in blood-pressure. The diet should also, as far as possible, be so planned as to avoid intestinal fermentation. A general **quantitative reduction of food** will be found to accomplish the desired result much better than qualitative measures alone. The patient should be told to gradually reduce the quantity of food until he finds the minimum on which he can maintain his bodily and mental vigor. For breakfast, some toast and tea and an egg; vegetable soup and some pudding at lunch; for dinner, fish, a couple of vegetables, and stewed fruit. If later at night more is wanted, a glass of milk or a bowl of bread and milk may be had. Meat may be used in small amounts; but if the patient can get along without it, so much the better. It is also generally recommended that as little salt as possible be used. In the

early stages it may not exert any particular action, but later in the disease it may have to be omitted. Tea and coffee in excess, liquor, and tobacco should be interdicted when possible. If complete abstinence cannot be procured, moderation should be enjoined. As long as the heart remains competent, water may be taken freely in order to increase elimination. When the heart begins to fail it will then be necessary to restrict within moderate limits the amount of fluid taken.

Following **diet** recommended: While dressing, 5 to 10 ounces of hot water containing 10 to 20 grains (0.6 to 1.2 Gm.) of either sodium sulphate, potassium citrate, sodium phosphate or carbonate, or similar alkaline or neutral saline, according to nature of case. Half an hour later, breakfast: Large plate of fruit, and milk or cream, followed by abundant cereal and milk with bread and butter. Five hours later, dinner: Not more than 4 ounces of meat or fish (quite fresh); large plate of green vegetables; potatoes sparingly; perhaps a taste of sweets. Five hours later, evening meal: Similar to breakfast; succulent vegetables may replace fruit, and macaroni or a similar dish be substituted for cereals. Thirst and hunger between-times may be satisfied by water and fruit, taken one hour before a meal or during night. Alcohol, tea, coffee, cocoa, and kola prohibited. Later, an occasional egg may be given at breakfast or supper. Gentle and regular exercise twice daily. T. A. Williams (Monthly Cyclo. and Med. Bull., Nov., 1911).

The writer recommends the following method: 1. **Rest** for the whole body, and particularly for any organs specially involved in sclerotic process. 2. **Diet** such as will avoid all digestive disturbances. 3. **Judicious restriction of fluids**. 4. **Systematic hydrotherapy, carbon dioxide baths or electric baths**. 5. **Iodides** only where angina pectoris, syphilis, or eye affections due to sclerosis of

retinal artery. 6. **Diuretin**, especially valuable in angina pectoris and tobacco heart; lowers blood-pressure markedly after some weeks' administration. Von Noorden (Post-Graduate, May, 1913).

The **few protein diet treatment** advocated by the writer consists of such drugs as are indicated in the individual case and in the **removal from the dietary of all meat, fish, eggs, and stock soups**, the administration of serial doses of **castor oil**, and the institution of a course of physical training suited to the individual. The **proteins are then returned to the diet one at a time**, beginning with cheese, which seems to be the safest of all. **Fruit, vegetables, bread, butter, and cereals are allowed without restriction**. This diet, "**few protein**" diet, in contradistinction to the "low protein" diet of other writers, is founded upon the belief that damage is due to protein poisons that are specific to the individual, and that if they are harmful at all, small quantities may be nearly as bad as larger amounts. The discovery of the proper diet must depend upon study of the particular person. The offending protein may be one that has been abused, and often enough it may be the one most craved by the patient when it is taken away. L. Faugères Bishop (Med. Rec., Sept. 20, 1913).

Exercise should be taken in moderate manner; it is a great mistake to interfere too much with the activity of the patient. **Moderate open-air exercise** is of the greatest value; this may be taken in the form of golf, horseback riding, walking, moderation again being the main point. What should be avoided is overstrain, sudden exertion, and overfatigue, these being certainly harmful. Although the primary effect of exertion is to elevate the systolic pressure, this increase is transient and is followed by a subsidence of pressure

to the original level or even to a slight diminution.

Baths of various sorts have been recommended, but as the end usually desired is a **free sweating** the particular method by which that result is obtained is not of great importance. The immediate effect of the above is to produce a drop of from ten to twenty points in the systolic pressure. This reduction is, as a rule, quite transient, but it will be found that the general symptoms seem much improved by the treatment. Although the blood-pressure may not be permanently lowered, yet the baths aid apparently in preventing the sudden rises which may result either in discomfort or danger to the patient.

The writer praises the results of treatment of arteriosclerosis at **Evian-les-bains**, in Savoy, France, owing to the skilled supervision now exercised over patients at that resort. Baup (*Paris méd.*, May 18, 1912).

Sufficient water or other liquid should be used to relieve thirst, but no more. Large amounts of fluid should not be taken, as the blood-pressure is thereby increased. The **warm, full bath** dilates the capillaries and lowers the blood-pressure; five minutes is a sufficient time. Cold bathing is injurious; swimming is not allowed because the cold water contracts the superficial capillaries, which when combined with the violent exercise may raise the blood-pressure dangerously high. It is not improbable that many of the cases of drowning ascribed to "cramps" are really due to cerebral hemorrhage, angina pectoris, or some other cardiovascular lesion induced by the greatly increased blood-pressure while swimming. C. W. Watson (*Jour.-Lancet*, Mar. 15, 1914).

In the **carbonic acid brine baths** the salts in solution exert more action than the gas bubbles. These baths

are best given at 32° to 34° C. and the cold bath is reserved for cases with subnormal intravascular pressure with a flaccid arterial wall. Slowing of the pulse is constant and important and is due to a lengthened diastole, thus resting the heart muscle. J. H. Honan (*Med. Rec.*, Feb. 5, 1916).

In plethoric subjects **venesection** is often a life-saving measure, especially when vertigo is accompanied by congestive headache and a flushed face. In such cases Allbut recommends this procedure once or twice a year. Women stand it better, as a rule, than men.

Of the drugs used some of the most important are the **saline cathartics** taken every morning before breakfast, as they not only bring about elimination but depletion as well. Two or three watery movements a day should be produced. They tend also to reduce the attacks of pseudo angina pectoris where these occur as a complication of arteriosclerosis.

The spasm is, in the great majority of cases, of toxic origin, and attention should be directed to the lessening of this toxemia, which is generally recognized to be due to nitrogenous bodies. In the intestinal tract certain bodies, of the aromatic series, are produced by the decomposition of proteid materials, and these, being absorbed, may, either by direct action on the vessels or in some less direct way, produce vasoconstriction. These poisons must first pass through the liver, and, if this organ be active, may be destroyed there and do no harm. It seems to be especially the proteid of meat and eggs that produces most toxins. If the toxins once reach the blood they are chiefly got rid of by the kidneys. Hence it is that Huchard puts, as the second most important factor in the production of the presclerotic stage of arteriosclerosis, insufficiency of hepatic and renal functions. Rudolph (*Brit. Med. Jour.*, Nov. 26, 1910).

The warning against the use of **chloral hydrate** in cardiovascular disorders given in numerous textbooks is unwarranted and has done harm in preventing the employment for hypotensor purposes of a drug both more efficacious and less injurious than the nitrites. Chloral is, with **bromides**, one of the best relievers of general and circulatory spasm. The sleep induced by chloral hydrate is characteristically followed on awakening by an abundant diuresis, as much as a liter of urine being passed in 6 or 8 hours, with manifest euphoria, relaxation from nervous tension, and lessened difficulty of breathing. A small dose of chloral suffices in some instances to overcome the inhibiting angiospasm and produce diuresis. **Chloral and caffeine** make sometimes the combination of choice for diuretic purposes. A. Martinet (*Presse méd.*, June 5, 1916).

Although various remedies have been brought forward as having a direct influence upon the vessel walls, the only one of value is **potassium iodide**. It has been stated that, in experimental animals, the giving of potassium iodide coincidentally with epinephrin will prevent the formation of arteriosclerosis. The iodide should be given freely in all syphilitic cases, 10 to 15 grains (0.65 to 0.97 Gm.) three times a day, and continued several months.

Potassium iodide is better than sodium iodide, since the former is more resolvent than the latter. In the initial stage the process may be arrested by potassium iodide and the solvent action of potassium may be combined with the tension-lowering effect of giving both salts simultaneously or alternately; 3 to 7 grains (0.2 to 0.45 Gm.) of **potassium iodide** and 5 to 20 grains (0.32 to 1.3 Gm.) of **sodium iodide** may be given in twenty-four hours. They should be administered during meals, two or three times a day, freely diluted with water and combined with some alkali, on account of the tendency of

acid drinks to liberate iodine, and so cause gastric disturbance. If the drugs are badly borne, **opium** or **belladonna** may be combined with them. Gouget (*Jour. méd. de Brux.*; *Brit. Med. Jour.*, Oct. 17, 1908).

The writer gives **potassium iodide**, from 1 to 3 Gm. (15 to 45 grains) in twenty-four hours, continuing this for months and years with intervals of a week each month. He orders at the same time a drastic purgative to promote the elimination of the iodide. Cardiac hypertrophy with high arterial tension and nocturnal polyuria with lesser density of the urine are signs of diffuse arteriosclerosis. **Brine baths, alcohol rubs, and tepid douches**, by soothing the nervous system, favor the elimination of waste. The practitioner should seek to ward off the impending uremia, asystole, or cerebral insufficiency, and treat them with the greatest energy if already developed. Lancereaux (*Bull. de l'Acad. de Méd.*, June 2, 1908).

Lancereaux and Paulesco have reported excellent results from the use of **iodothyryn**, claiming that it not only diminishes arterial tension, but actually lessens the rigidity of palpable arteries. The employment of this drug, as well as that of the uncombined **thyroid extract**, is certainly rational, for, as is well known, the removal of the thyroid gland is followed not only by increased viscosity of the blood, but also by arteriosclerosis. F. P. Henry (*Monthly Cyclopedia and Med. Bull.*, June, 1908).

Iodides have a marked hypotensive action in high blood-pressure, without arteriosclerosis. In advanced arteriosclerosis with high blood-pressure iodides have no hypotensive action. To produce a beneficial effect in hypertension, 10 grains (0.65 Gm.) of **potassium iodide** should be the initial dose. This should be rapidly increased if necessary. Organic iodides—in the therapeutic doses recommended—contain too little iodine to be efficient. Only in cases in which iodides are contraindicated by alimentary disorders should **sajodin** be substituted in corresponding doses.

Matthews (Edinburgh Med. Jour., Mar., 1911).

Cases illustrating the danger of giving iodide of potassium when the hypertension is accompanied by abnormally low viscosity of the blood; when the heart or kidneys have little or no reserve force; when the kidneys are unquestionably insufficient, and, above all, when a hemorrhagic tendency is manifest. Such patients are constantly menaced by uremia and cerebral hemorrhage. But outside of these conditions **potassium iodide** is liable to render valuable service. Martinet (Presse méd., Nov. 11, 1911).

Many drugs have been used to directly influence the blood-pressure, but proper dieting and hygiene are much more important. As to the propriety of using such drugs there is much discussion, many holding that the high blood-pressure is a compensatory process; that it is an attempt to maintain an adequate speed of capillary flow through the kidney or other organ which would otherwise be impossible. There is, however, no certain correspondence between the amount of urine secreted and the degree of blood-pressure. If a **nitrite** is given to lower blood-pressure there frequently will be an increase in the amount of urine. Some physicians refuse to use drugs to regulate the pressure, on the ground that the tissues have become accustomed to the new standard, and that it would be unwise to interfere. That this view may be correct in some cases is the fact that occasionally there may be a patient who is much more disturbed and uncomfortable with the pressure lower than it was before. Of the drugs given **nitroglycerin** is often effective, but according to Osler it is rarely given in large enough doses, and even then is liable to be very transient in its effects. It is best given in solutions freshly

made, in doses of 1 to 3, 4, or 5 minims (0.06, 0.18, 0.24, or 0.3 c.c.) of the 1 per cent. solution three or four times a day. In crises of high tension larger doses may be given. It does not seem to do any harm, but as individuals react so differently to the drug it is well always to test it upon each patient. Good results are frequently not obtained until much larger doses are given than are usually employed. **Nitrites** may be of value in those patients in whom the high pressure is not wholly due to anatomical changes, but also to a certain spastic condition of the vessel walls. This represents the irritative effects of the circulating toxins. For routine work **sodium nitrite** is the best. Its action is more prolonged and is not followed by the unpleasant cerebral disturbances that frequently result from the use of nitroglycerin. In doses of 1 to 4 grains (0.065 to 0.26 Gm.) every three to four hours it may be of great service. Small amounts should be given and be gradually increased until the desired effect is obtained.

In *insomnia* due to arteriosclerosis the writer gives **nitroglycerin** for long periods in doses of $\frac{1}{150}$ grain (0.0004 Gm.), 1 tablet two hours before retiring, another at bedtime. Sometimes the patient becomes accustomed to the drug and it is necessary then to administer **sulphonal** or **trional**, although this should not be done if it can be avoided. Friedeberg (Klinisch-therap. Woch., Oct. 21, 1900).

In cases with persistent hypertension the writer uses a modified Lauder Brunton draught:—

℞ *Sodii nitritis* 3 Gm. (45 grs.).
Sodii bicarbonatis (C. P.),
Potassii nitratis,
 āā 32 Gm. (1 oz.).
Aquæ . . . q. s. ad 132 Gm. (4 fl. oz.).

M. Sig.: Shake well. One teaspoonful in a goblet of hot water before breakfast.

In rebellious cases, usually associated with sclerosis, the remedy is given before each meal. In many cases of uncomplicated hypertension small doses of **chloral** (0.3 Gm., or $4\frac{1}{2}$ grains) will, with attention to the digestive system and thorough emptying of the intestinal tract by means of **salines** and the use of **alkalies**, cause a decided drop of blood-pressure and relief of symptoms. Pounding, irritable hearts with hypertension, with or without vertigo and discomfort referable to the head, are, as a rule, relieved by the administration during two or three weeks, three times daily, of from 1 to 1.5 Gm. ($15\frac{1}{2}$ to 23 grains) of **strontium bromide** with from 2 to 4 drops (0.12 to 0.24 c.c.) of tincture of **veratrum viride** or of **aconite**. H. L. Elsner (Amer. Jour. Med. Sci., Jan., 1911).

In disturbances of digestion and arteriosclerosis **diuretin** acts as a specific remedy against abdominal pains, in such cases; from 2 to 3 Gm. (30 to 45 grains) are to be given daily. Tincture of **strophanthus**, in doses of 4 to 8 drops, given twice or three times daily, has also had good results. A. Pick (Med. Klinik, May 12, 1912).

Although hypertension is present, yet that does not indicate that all treatment should be directed to the vascular system, as the heart may be in need of attention. When there are indications of an inadequate ventricle, as shown by the existence of edema, gallop rhythm, or the occurrence of attacks of acute dyspnea, it may be necessary to use **cardiac tonics**. **Digitalis** is not necessarily contraindicated by the high pressure, as it is seldom that this drug increases the pressure sufficiently to endanger the vessel wall. Not infrequently the pressure will fall after its administration, probably because the drug brings about a better oxygenation of the blood by bracing up the pulmonary circulation.

Diuretin, or **theobrominisodiosalicylate**, is the most effective and most used, being employed in doses of 10 to 15 grains (0.65 to 1 Gm.) three times a day. So prompt and satisfactory is its action in cases of this kind that its use has been recommended as a means of diagnosis in doubtful cases, just as we use quinine in suspected malaria and mercury in syphilis. Its effect depends on its powerful action in overcoming the vessel spasm and dilating the arterioles so that they allow a greater flow of blood to the sclerosed areas. Of diuretin it is also suggested by Buch that it may neutralize the effect of some toxic agent which tends to irritate the vasomotor centers and cause contraction. Akin (Jour. Amer. Med. Assoc., June 5, 1909).

The larger his experience and the more he watches cases of pronounced arteriosclerosis, especially in men and women past middle life, the less frequently does the writer prescribe either **digitalis** or the iodides. If a cardiac tonic or stimulant is required, **strophanthus**, **caffeine**, and **nux vomica** are preferable by far and are not liable, in small or moderate doses, to do positive injury. They require also judicious watching and suppression at times, but not to the same degree as **digitalis**. To lessen supertension where it is clearly indicated by reason of headache, fainting attacks, pallor, and general nervous irritability **sweet spirit of niter** in small or moderate doses, added to water, is the least injurious and most useful drug the author knows of, not excepting **nitroglycerin** and the **nitrites**. Beverly Robinson (N. Y. Med. Jour., Aug. 19, 1911).

Case histories illustrating the truth of Dr. James MacKenzie's statement that the vast majority of patients in whom **digitalis** acts with such marvelous effect in slowing the rate and improving the condition are those affected with auricular fibrillation. The reason that **digitalis** has acquired such a reputation as a cardiac drug is due to the peculiar susceptibility of patients with auricular fibrillation, and practically all recorded

cases illustrating the remarkable effects of digitalis are cases of auricular fibrillation. Hearts with the normal rhythm are seldom so sensitive, and in them there is not the same tendency to slowing of the rate. The cases also sustain the personal view that a large proportion are examples of damage to the thinner and lighter, and perhaps more susceptible, portions of the heart muscle composing the auricle, by the products of intestinal putrefaction, while the heavier and more substantial ventricle has escaped proportionate involvement. Bishop (N. Y. M. J., Sept. 9, 1911).

Various symptoms among those enumerated early in this article require individual attention as they arise. Iydston has found that **thiosinamine**, $\frac{1}{8}$ grain (0.013 Gm.) 3 times daily gradually increased to 1-grain (0.06 Gm.) doses, will greatly relieve the morbid process.

Partial relief from *headache* and *dyspnea* is frequently afforded by **thiosinamine**. Daily doses of 0.06 to 0.10 Gm. (1 to $1\frac{1}{2}$ grains), by injection or ingestion, produce no untoward effects. The blood-pressure descends only after prolonged administration. Rénon (Bull. de l'Acad. de méd., Apr. 25, 1911).

Theobromine sodium salicylate (**diuretin**) is very effective in relieving the *sweet taste* of arteriosclerosis. On suspension of the drug in a personal case, the disturbance returned, but was again cured in the same way, and the patient now takes this drug continuously and has been free from the trouble for a year. Similar benefit was realized in another case in which the patient complained of attacks of pain in the tongue of arteriosclerotic origin. A. Müller (Zentralbl. f. innere Med., July 15, 1911).

In addition to the more specific methods of treatment as given above, there are various general factors to be considered: Naturally the removal, as far as possible, of the underlying causes.

An extended holiday or a let up in work—not a complete cessation, however, unless there are signs of cardiac failure or marked mental symptoms—should be recommended. The patient should be told that there may be many years of fairly active life to come to his lot if he will ease up his existence and live moderately in all things.

For the wealthy, a course at **Royat, Aix-les-Bains, Carlsbad, or Marienbad** sometimes proves very efficient, especially if the dietetic measures and graduated exercise in the open air which form part of the treatment are carefully carried out. The pessimistic views of Osler concerning the therapeutic value of mineral springs have been shown to be unwarranted, since the researches of Ramsay showed the radioactive properties of **radium** were due to the new element, *niton*, and that the waters of many springs owed the therapeutic value to the electrones of this element.

The writer recommends **radium** by emanation, inhalation, radioactive drinking waters, solutions of radium salts for drinking, emanation baths, and, by intravenous or subcutaneous route, the bromide or chloride of radium. It has absolutely no toxic effects and the dose in high blood-pressure is governed by the chronicity of the case and the involvement. In a series of 190 cases, the average systolic pressure was 190 and the average reduction was 40 mm. C. E. Field (Med. Rec., Jan. 22, 1916).

As we have seen, Sajous holds that we must differentiate three general factors in the etiology of the disease and that the ductless glands are participants in the morbid process. He therefore adjusts the treatment to each of the three types, as shown below.

Adrenal Type.—Such cases yield readily to measures calculated to re-

duce the functional activity of the adrenals. A less arduous occupation, abstention from meat, coffee, tea and alcohol (to lower the vascular tension) often suffice. If the vascular tension is high, the condition of the kidneys should be looked into. As a rule, at this time these organs are found normal, though some polyuria be present. **Spirit of nitrous ether** may then be used in small doses thrice daily to reduce the high tension if it fails to recede after a few days, and also small doses of **sodium bromide** and **chloral** on retiring if the tendency to insomnia persists.

The iodides at this stage are harmful. So are strychnine, digitalis and tonics in general, most of which stimulate the adrenals and aggravate the trouble.

Proteolytic Type.—Prophylactic measures, a **reduction of proteins**—eliminating meats and eggs—and other harmful food the patient may be indulging in too freely, are necessary. Acidosis is another harmful factor which a **vegetable diet**, by supplying alkaline salts, tends to counteract and gradually to eliminate. Although the arteries are already damaged, there occurs an active process of repair by insular sclerosis so disposed longitudinally as to preserve the contractile activity of the vessel to a remarkable degree.

It is of course irrational to give the iodides in cases in which the thyroid secretion laden with iodine in organic combination is taking part in the cellular destruction of the arterial walls. No remedies should be administered until the toxic factor, whatever that may be, dietetic, intestinal, bacterial, etc., is eliminated prophylactically. If, after a couple of months, the patient does not show the sense of well-being which usually follows well-addressed prophylactic measures, and still complains of neurasthenia-like symptoms, it is because catabolism and arterial degeneration are still proceeding, owing mainly to hyperplasia of the thyroid. Arsenic in small doses, say 3 minims (0.18

c.c.) of **Fowler's solution**, *t. i. d.*, as shown by Mabile and confirmed by Ewald, Heinrich Stern and others, will then gradually reduce the thyroid erethism. In cases showing actual hyperthyroidia, or larval Graves's disease, **ergotin**, or the **coal tars**, are helpful to contract the vascular supply of both the thyroid and adrenals and thus inhibit the secretory activity. It should be remembered that **rest** is an important feature wherever exuberant activity of the ductless glands is in order.

Denutrition Type.—The treatment here is precisely the opposite of that indicated in the foregoing forms. Organotherapy, provided **thyroid** and **adrenal gland** and any other organic product used be given in *small doses*, is of very great value. The **iodides**, also in small doses, **digitalis** and **strophanthus** are all exceedingly helpful. A **sustaining diet** here is important. Besides the thyroid and adrenal preparations already mentioned, some pancreatic product such as **holadin** should be added to facilitate intestinal digestion, sustain tissue life and contribute, with the other organic products administered, to the defensive resources of the organism. C. E. de M. Sajous (N. Y. Med. Jour., May 26, 1917).

Emaciation sometimes precedes arteriosclerosis, the loss of weight being at times 60 pounds. The subject may appear in the best of health. It could not be due to war factors except in a few cases, the author having observed it before the war. It appears to be readily controlled by **supernutrition**. The diet should be rich in calories and be well balanced. The only drug recommended is **iodine**, the too protracted use of which, however, may itself lead to emaciation. Kiralyfi (Wiener klin. Woch., Oct. 14, 1920).

GUTHRIE McCONNELL,
Philadelphia.

ARTHRITIS. See JOINTS, DISEASES OF.

ASAFETIDA is a gum procured by incising the living root of *Ferula fetida*, a perennial herb of the natural order Umbelliferae, native of Persia and Afghanistan. The exuded gum is dark yellow or reddish in color, occurs in regular masses or tears, is very soluble in alcohol, and forms a milky emulsion on trituration with water. Its odor resembles that of garlic and is penetrating and persistent. The principal constituent of the drug, and that to which its odor is due, is a volatile oil, consisting in part of hexenyl sulphide, hexenyl disulphide, pinene, and cadinene (Kraemer); it also contains about 60 per cent. of a resin; a gum; ferulaic, malic, acetic, formic, and valerianic acids.

PREPARATIONS AND DOSES.—

Emulsum asafetida (emulsion of asafetida, milk of asafetida), containing 4 per cent. of the drug. Dose, $\frac{1}{2}$ to 1 ounce (15 to 30 c.c.).

Pilula asafetida (pills of asafetida), each pill containing 3 grains (0.2 Gm.) of asafetida. Dose, 2 to 4 pills.

Tinctura asafetida (tincture of asafetida), containing 20 per cent. of asafetida. Dose, $\frac{1}{2}$ to 1 dram (2 to 4 c.c.).

Suppositories of asafetida, unofficial, containing the equivalent of 40 drops (2.6 Gm.) of the tincture.

Plaster of asafetida, unofficial, useful as an antispasmodic and mild counterirritant.

PHYSIOLOGICAL ACTION.—Asafetida is a stimulant to the brain and nervous system, a powerful antispasmodic, a gastric stimulant and carminative (imparting a sense of warmth to the stomach), a laxative, diuretic, diaphoretic, emmenagogue, and aphrodisiac. It is also a stimulating expectorant. Large doses cause vomiting and purging, nervous phenomena, and burning urination. The drug, or its volatile oil, is eliminated by the urine, sweat, and breath.

THERAPEUTIC USES.—The drug is serviceable in flatulence, especially in old people and children. In **infantile convulsions** it is highly useful, given by rectal injection. In the **tympanites of typhoid fever** asafetida is an effective remedy, given by enema. In **hysteria** and **nervous exhaustion with indigestion** and flatulence, as a stomachic tonic in **dyspepsia** with flatulent colic, and as an expectorant in

chronic bronchitis, it is also of great value. In **whooping-cough** it acts both as an expectorant and antispasmodic. W.

ASCARIS LUMBRICOIDES.

See PARASITES, DISEASES DUE TO.

ASCITES.—While this term means dropsy of the abdominal cavity, it is but a division of the general subject of edema, which, therefore, will first be considered.

EDEMA.

DEFINITION.—The term edema, signifying swelling, is applied to a number of conditions, sometimes in a merely explanatory sense, while in other instances it has reference to a particular feature of a disease, or, with a modifying word, denotes the disease itself. Solid edema, for example, is applied to myxedema, or to swellings which contain a thick lymphoid material. Malignant edema is described as a specific disease. In its common acceptance, however, the term refers to an abnormal amount of serous fluid in the areolar tissues of the body, and results when the transudation from the vessels exceeds the absorption by the lymphatics. The term dropsy is applied to edema of the serous cavities. Anasarca is a universal edema of the subcutaneous and intermuscular spaces. Edema and dropsy are synonymous terms.

ETIOLOGY AND PATHOGENESIS.—Although the underlying conditions that give rise to edema are, in a great measure, undetermined, recent investigations and experiments have made material additions to our knowledge of the subject. The factors concerned with lymph formation are to a certain extent operative in the production of edema. A few preliminary statements, therefore, regarding lymph will be appropriate.

Lymph is a fluid which escapes from the blood-vessels, fills the intercellular spaces, and is absorbed by the lymphatics and blood-vessels. The quantity present in the tissues depends upon the amount escaping from the blood-vessels and the amount absorbed by the lymphatics. Different views are held with regard to the processes by which this escape is effected. Stengel holds that the outflow takes place through a more or less permeable capillary wall as a consequence of direct filtration, osmosis, and probable secretion. Hektoen states that lymph formation is the result of diffusion, filtration, and, if Heidenhain be correct, an active secretory function of the capillary endothelial cells. Bainbridge, reviewing the recent experimental work of others and referring to his own, believes that nothing is known concerning the physiological variations in the permeability of the capillary walls, regarded under normal conditions as constant, but that this is not so in disease. His conclusions are that the mechanical theory held by Cohnstein and Starling, that lymph formation normally depends upon intracapillary pressure and permeability of the capillary wall, holds its ground; that there is a growing tendency to attach more importance to vital changes in the capillary endothelium, and that the experiments of Asher and others have established the connection between lymph production and tissue activity. He further states that Starling's physical views were challenged by Asher, but that the experiments of the latter, with those of Hooker and Mendel, are not yet complete and would appear at present to confirm rather than refute the views of Starling.

Basing their views, in a measure,

upon the theories held with regard to the cause of lymph production, recent writers consider that filtration from pathological variations in blood-pressure, transudation from increased permeability of the capillary walls, and osmotic and other processes depending upon changes in tissue activity are the main sources of edema. Additional supposed factors are changes in the composition of the blood, decrease of elasticity and pressure in the tissues, obstruction to the flow in the lymphatics, the action of bacteria and toxins, and chemical changes. All of the last mentioned are more or less connected with the others in the relation of cause and effect, and it is necessary to consider them in detail.

Filtration through the arteries or capillaries as the result of active hyperemia is rare, and would occur only when the veins are obstructed; but it is difficult to escape the conviction that the dropsy of passive hyperemia is not partly due to mechanical filtration from direct pressure within the vessels. The fact that in cardiac disease a certain amount of intracapillary pressure is probable, and that the edema appears first in the most dependent portions of the body, is an argument of some weight in favor of the view expressed.

The increase of permeability in the capillary walls is advocated by many as one of the most important causes of edema, and as a probable factor in all edemas. Indeed, this condition, rather than filtration, is stated to be the result of long-continued passive hyperemia, the pressure of which is supposed to set up nutritive disturbances and diminished elasticity of the extravascular tissues. Hydremic plethora, so called, although it occurs in the early stages of cardiac dropsy, is not sufficient,

when experimentally produced, to cause edema. Bolton's experiment, in which he produced cardiac edema by tying off portions of the pericardial sac and compressing the heart, demonstrated that neither the venous nor the arterial pressure was materially affected. The veins apparently accommodate themselves to the increase of blood. The deduction is that passive hyperemia causes increased permeability with transudation rather than filtration from mechanical pressure, and that the effect is brought about by deficient oxygenation, and imperfect nutrition of the capillary walls. In the same manner local edema may follow local passive congestion.

Another cause of increased permeability is a change in the composition of the blood, which acts indirectly and is brought about by the action of toxins and bacteria, which, in addition to their influence upon the blood itself, stimulate the endothelial cells to excessive or perverted function. Such may be the case with chronic infections, and certain cachexias, such as malaria. The chemical changes referred to—chiefly the lack of oxygen—are supposed by Loeb to cause an increase of osmotic pressure in favor of the tissues over the blood and lymph.

A good deal of weight is being attached at the present time to the influence of tissue activity upon the production of edema, and the subject will be referred to in a different connection. Decrease of tissue elasticity and pressure is regarded by some as the main cause of edema *ex vacuo*, observed in the subarachnoid spaces of the brain and other portions of the central nervous system. Lymphatic obstruction does not usually cause edema on account of the free collateral circulation; but when large trunks are

affected, or when there is complete occlusion of the lymphatics of a part, a pure lymphatic edema may occur, and be hastened by increased lymph production. Bainbridge, summing up his conclusions, believes that cardiac dropsy is due to a disturbed relation between the vascular system and the lymph, while renal dropsy is due primarily to changes in the relation of the tissues to the lymph. He further adds that renal dropsy is due, first, to a scanty excretion of urine; secondly, to a retention of sodium chloride and possibly other salts, and, thirdly, to increased catabolism in muscles due to partial or complete loss of control over muscular metabolism by the kidneys. This catabolism brings about an accumulation in the muscles and tissue-spaces of waste products (metabolites). These metabolites, by a process of osmosis, attract water from the blood into the tissue-spaces. When the fluid in the tissue-spaces cannot be carried off by the lymphatics, edema appears.

The same writer explains the dropsy of anemia, first, by the low oxygen-carrying power of the blood, resulting in malnutrition of the capillary endothelium and consequent increased permeability; and, secondly, as in chlorosis, by the increase in volume of the blood, with resulting hydremic plethora. The venous and capillary pressure is raised, and increased filtration of lymph occurs. In other forms of anemia, without hydremic plethora, edema is supposed to be largely the result of increased capillary permeability.

[The experiments and clinical observations made by Widal, Lemierre, and Cotoni (Semaine médicale, July 12, 1911) offer an additional proof of the influence of sodium chloride in the production of dropsy. They assert that the ingestion of large amounts of sodium bicarbonate

checks the elimination of sodium chloride, and thus promotes the retention of water. The dropsy occurring in diabetes after such doses of sodium bicarbonate can be thus explained. The discontinuance of the bicarbonate causes the dropsy to disappear, while its use does not seem to produce any serious or permanent disturbance of nutrition. The bicarbonate may not be the only substance possessing such a property. W. S. GORDON.]

Salt retention is an important factor in paroxysmal edema. Although the kidneys can take care of 2 to 3 Gm. (30 to 45 grains) of sodium chloride daily, any increase in the demand for this salt excretion actually reduces, at least temporarily, their capacity even below this amount. The marked therapeutic value of **reduced salt diet** and **free catharsis** is emphasized. W. W. Palmer (Arch. of Internal Med., Feb., 1915).

In the edemas observed in nervous disorders, such as angioneurosis, neuritis, neuralgia, hemiplegia, and organic disease of the cord, increased permeability of the capillary walls and transudation are regarded as direct causes. At the same time, imperfect absorption from vasomotor disturbances may have its influence, and changes in the tissues are in all probability involved. Whether the so-called hereditary edemas are due to congenital excess of vascular permeability is a question. Hektoen refers to the frequency of edema in arteriosclerosis; but inasmuch as edema often occurs without sclerosis, he suggested the term *angiopathic edema*. Thoma claims that in a certain proportion of cases angiosclerosis is a cause. Along with the actual condition of the arteries in these cases, we must take into consideration the condition of the heart and kidneys, and the direct processes, already mentioned, by which fluid escapes from the blood-vessels.

Martin H. Fischer, basing his conclusions upon experiments, holds that "in the variable affinity of colloids for water we have an explanation of many of those physiologic phenomena which are characterized by a storage or migration of water." He concluded, moreover, that alterations in the permeability of the vessel walls have never been demonstrated experimentally, and all efforts to produce states of edema through simple increase in blood-pressure have failed. The results of prolonged intravenous injection at high pressure of enormous amounts of various liquids are explained more easily, in his opinion, by changes brought about in colloids than through simple pressure effects.

Jacques Loeb, some years ago, holding that edema was due to changes in the tissues themselves, tried to find in an increase in the osmotic pressure of the tissues the cause of the increased absorption of water; but while the explanation was inadequate, the experimental facts brought out are of permanent value and should have received more recognition.

The increased affinity of the colloids is caused by the fact that various substances (particularly acids) capable of greatly increasing the affinity of colloids for water are not removed as they should be, or are produced in abnormal amounts; and colloids having little affinity for water are changed into such as have a greater affinity. The former of these two propositions is the only one discussed.

To prove his proposition it must be, and can be, proved that protoplasm is colloidal; that in the variable affinity of colloids for water we have a force of sufficient magnitude to account without strain for the maximum amount of

water ever found absorbed by tissues in a state of edema, and that conditions leading to an increased affinity of their colloids for water exist in the tissues under circumstances associated with the development of edema. With the exception of alkalies, acids, including carbon dioxide, are the most powerful substances thus far known for increasing the affinity of colloids for water, and it is either the retention or the abnormal production of acids in the tissues that causes the development of edema. Glaucoma, urticaria, and diapedesis are explained on this theory.

When edemas similar to those of heart lesions and thrombosis are produced in frogs, the acid reaction is so high that litmus is changed by the muscles. In nephritis, poisons are produced, and affect the tissues, altering their metabolism so that acids are produced which influence the colloids.

Urticaria (local edema) is benefited by calcium salts because they increase the calcium content of the tissues and lessen their tendency toward a development of these edemas.

Moyer S. Fleisher, Daniel M. Hoyt, and Leo Loeb to determine whether calcium chloride has the same inhibitory action upon the production of edema, especially ascites, in experimentally produced hydremic plethora as it does upon diuresis and the secretion of fluid into the intestines, reach the following conclusions: "In contradistinction to the decreased elimination of fluid through the kidneys and intestines, addition of calcium chloride to the sodium chloride solution increases markedly the transudation of fluid into the peritoneal cavity. To a certain degree the urine and ascites may be said to increase in an inverse proportion."

This effect is brought about by diminishing the amount of urine and by increasing the ascites independently of the action of calcium chloride upon the kidneys; but further investigation is needed to determine whether there be a direct action upon the endothelial cells of the peritoneal cavity. It is further established by these observers that more fluid is found in nephrectomized animals, and that calcium chloride does not exert its specific effect on the quantity of peritoneal fluid through a lowering of blood-pressure.

Among the possible causes of extensive ascites are small solid tumors of the ovary. Pleural effusions may be produced by an extensive ascitic accumulation—an association that may lead to a false diagnosis of pleural and peritoneal tuberculosis. Cures of both pleural and peritoneal effusions may result from excising a benign tumor. Cabot (Pub. of Mass. Gen. Hosp., Jan., 1913).

Epidemic Dropsy of India.—This form (Journal American Medical Association, vol. lvii, p. 826, 1911) first attracted attention in Calcutta in 1877. After apparently subsiding, cases appeared in Calcutta in 1901, and in the following decade the disease was investigated by the government. There was a resemblance to beriberi. The main symptom was marked edema, mostly of the skin and subcutaneous tissues. The serous cavities may be invaded, and neuritis occur. According to Grieg, the malady resembles "ship beriberi," and also the "prison beriberi" of the early nineteenth century. It is non-infectious. Malnutrition from dietetic restrictions appears to be the cause of the disease.

The writer observed in Northern Africa cases of a low febrile state with vomiting and diarrhea, followed

suddenly by anasarca, a peculiar eruption, acute anemia and intestinal disturbances. It is the first time, he thinks, that this epidemic dropsy has been known in northern Africa. The necropsy findings in the liver and kidneys resemble those of amyloid degeneration. He is convinced of the infectious origin. Leporim (Policlinico, Feb. 10, 1918).

Edema occurred in the course of infectious disease in a number of cases observed by the writer during the war. There was also slowly progressive weakness, with slight yellowness of the skin and pallor. Occasionally pains in the legs were observed, as well as scorbutic symptoms and severe intestinal disorders. It was encountered almost exclusively in poorly nourished persons driven to hard work, and was similar to beriberi. Cure followed a more liberal diet in substances known to contain vitamins. Jürgens (Berl. klin. Woch., Feb. 28, 1916).

Pathologic and Microscopic Anatomy.—The extent and situation of edema depend upon circumstances. It may manifest itself in a very limited space, as in urticaria and hydrocele, or involve nearly all of the organs and tissues of the body. The transudate is found first in the lymph-spaces or interstices of the tissues, producing a more or less uniform swelling, which leaves a temporary indentation on pressure. Solid organs are rendered lighter in color, less dense, and moister than normal, and when the tissues are cut there is an exudation of liquid. The characteristic features of edema are best observed in the soft organs and submucous and subcutaneous tissues. The tissue elements are seen by the microscope to be more or less separated, and the cells may become diseased from pressure.

Nature of the Fluid of Edema.—The fluid is usually clear, colorless, of low

specific gravity, and alkaline. It contains a smaller amount of proteids—especially fibrinogen—than blood-serum; also a few leucocytes and red cells. In serous cavities desquamated and degenerated endothelial cells and fat-drops are apt to be present, and milkiness may be due to precipitated albumin. Morbid products from the blood may be found. Inflammatory exudates are usually turbid, often bloody, of high specific gravity, rich in proteids, and sometimes contain a good deal of fibrinogen.

[In the interesting case of *pseudochylous ascites* reported by F. P. Henry (New York Medical Journal, July 1, 1911), the fluid contained serum-albumin, serum-globulin, a small amount of nuclein, very little fat, a notable amount of lecithin, and traces of sugar, probably dextrose. The ash consisted of sodium chloride, phosphates, and sulphates. The author quotes the exhaustive researches of Wallis and Schölberg to prove that the milky appearance of the fluid is due to a mixture of lecithin and serum-globulin, and states that previous to 1860 only 25 cases of milky effusion into the peritoneum had been recorded, and 171 cases since, including 3 cases reported by Wallis and Schölberg. Such effusions must, therefore, be regarded as rare. W. S. GORDON.]

Results of Edema.—These may be trivial, but at times are serious, as in edema of the larynx, lungs, brain, and other organs. Degeneration of cells may occur, and connective-tissue changes, as in elephantiasis. Mechanical pressure may seriously interfere with the function of certain organs, while ischemia is common, and reduces the vitality and resisting power of the structures involved.

It is evident, from the various views expressed, that the mediate and immediate causes of edema are not fully understood; but much light has been thrown upon the subject, and we are

nearer to an explanation of the complex processes involved in the production of dropsy. The consideration of the ordinary forms of edema and their *treatment* will be found under the diseases of the organs and structures in which it occurs. The subjects following may, however, fall appropriately under the heading of Ascites, treated below.

Starvation Edema.—The recent war has, through the widespread starvation it produced, given rise to a large number of such cases.

The edema of war or of prisoners' camps (U. S. Naval Med. Bull., July, 1918), occurred during the Napoleonic campaigns, the siege of Paris, and in the concentration camps during the Boer war, when it was known as epidemic edema (Maliwa). Falta, of Vienna, in a review of the subject mentions that the disease was well known in Russia during famines before the war, and that the expression "swollen from hunger" was current in the affected districts. During the war the first record of the disease was in 1915 by Strauss, who described "the hunger disease" in Russian Poland and Galicia, where the poor were much exposed to war epidemics and had an insufficient and monotonous dietary. It has also been called "potato disease" and "salt hunger."

A form of edema was observed in 110 cases in certain towns in Poland from insufficiency of food following German occupation. The salient symptoms were, besides the edema, muscular weakness, intestinal disorders, mental depression, dimness of vision, disappearance of sexual impulses, and alterations in the blood and urine. The edema was sometimes limited to the lower limbs, but more often spread over the whole body, involving the face, and especially the eyelids, sufficiently in some to interfere with vision. It sometimes led to bursting of the skin with serous exudation. The swollen, cold skin was painful when pinched up. The condition lasted 1 or 2

weeks in some, in others months, and sometimes recurred. Eight patients succumbed. Budzynski and Chelchowski (Jour. of Trop. Med. and Hyg., June 15, 1916).

In August, 1915, when the City of Mexico had been the center of military operations for nearly 3 months, there appeared numerous cases of edema in men, women and children with absence of albuminuria. The mortality was high, the patients dying in marasmus from heart failure. There were hypothermia, bradycardia, pains in the muscles and reduction of the reflexes. The red corpuscles count was below normal, and the hydremia was generally marked. In some cases there was proliferation of sclerous tissue around the arteries. The only food available had been vegetables, beets and spinach mainly. Landa (Gaceta Medica de Mex., Jan.-June, 1917).

Famine edema occurred among the prisoners of all nationalities who were fed on German rations only, in which fat and protein were very scant. When well established it is frequently complicated by a colitis, when the mortality is high. The condition commences as slight edema of the feet and legs, disappearing when the patient is recumbent. It can be cured easily in the early stages by sufficient diet.

The writer also saw some 20 cases of bilateral enlargement of the parotid glands. The latter were at no time hard or painful, but rather soft and doughy, the swollen regions being easily pinched between the finger and thumb. The condition was afebrile. F. A. Park (Bull. Can. Army Med. Corps, Apr., 1918).

TREATMENT.—The curative treatment of edema resolves itself into measures calculated to counteract the cause. The condition itself, however, demands attention to give the patient relief and prevent the morbid effects incident to the presence in the tissues of what amounts

virtually to a mass of foreign fluid. Rest, limitation of the amount of fluid ingested, and free movement of the bowels are the most important means in the treatment of obstinate edema. The bowels are acted upon by **Rochelle salt** in doses of $\frac{1}{2}$ to 1 ounce (15 to 30 Gm.) in about 4 ounces (120 c.c.) of water. This may be preceded by a moderate dose of **calomel**. **Digitalis** combined with **squills** and **calomel** is very useful. **Theobromine** is most effectual in the dose of 10 to 15 grains (0.65 to 1 Gm.) three times daily, given dry on the tongue and washed down by a draught of water. The use of diuretics requires care, however, for the kidneys may be the seat of acute or subacute inflammation, conditions which limit the employment of these agents. Next after the theobromine comes **sparteine sulphate**, the dose being from $\frac{1}{4}$ to 2 grains (0.016 to 0.13 Gm.) in twenty-four hours. **Caffeine** given in $7\frac{1}{2}$ -grain (0.48 Gm.) doses, three times daily for short periods, has also given good results. **Apocynum** (*q.v.*) in 10-minim (0.61 c.c.) doses, three times daily, has been highly recommended by Dabney and others in such cases.

The writer treats prematurely born infants with a tendency to edema by wrapping them in **oiled silk** instead of putting them in an incubator. Since he adopted this method of treatment two years ago, this syndrome has entirely disappeared from his service. The aim is to keep in the child's heat, and the infant is wrapped completely in the oiled silk, only its head protruding. H. Dufour (Bull. de la Soc. de Pédiatrie, Feb., 1910).

Baths—hot-air, vapor, or hot-water administered after the Mannheim plan—are a valuable auxiliary; so

is **massage**, which seems to aid in the absorption of the effused liquid.

Evacuation of the fluid, by means of the **trocar** in ascites, **incision** of the legs—or on the dorsum of both feet as advised by Rolleston—in edema of the limbs, or again **Southey's tubes** or the newer **lymphangioplasty**, afford considerable relief, besides enabling the patient to increase his fluid intake, if this had been previously restricted, thirst being sometimes very marked.

The obvious method of restricting the fluid taken by a dropsical patient is still a matter for debate; and just as the strict diet formerly employed in grave or composite cases of diabetes has been relaxed on account of its bad results, so with regard to the plan of restricting fluid in renal dropsy it has been thought that it may be a source of danger (Strauss). In the edema of acute nephritis **restricted fluid** appears to be the most satisfactory treatment, for it economizes the labor of the kidneys in the matter of excreting water, and so enables them to rest and recover. With regard to the edema of chronic nephritis, the very considerable differences manifested by different patients must be recognized. In some the kidneys are incapable of dealing with more than a restricted amount of fluid, whereas in others the kidneys show an ability to deal with an increased ingestion of fluid hardly below that of the healthy organs and yet there is edema. Rolleston (Brit. Med. Jour., Aug. 28, 1909).

Method of silk drainage, **lymphangioplasty**, for lymphatic obstruction causing chronic edema. The silk is passed under the skin for long distances, the needle being drawn out at intervals and introduced again in the same hole. The operation gives good results in solid edema or, rather, elephantiasis; the only mishap liable is from possible infection of the thread. In some of the cases on

record the threads were withdrawn on this account, but after the lymph had become sterile they were reinserted with ultimate success. M. Guibé (*Presse méd.*, Jan. 19, 1910).

Deprivation of salt is an important feature of the treatment. Widal, Lemierre, Javal, and others having found that edema could be produced in a suitable case by giving certain doses of sodium chloride. The most important theories as to the mode of action of this salt are: (1) that the kidneys are diseased and partly impermeable to chlorides; (2) that the osmotic power of the blood is sufficiently increased to enable its plasma to permeate to an abnormal degree the endothelium of the capillaries.

Be this as it may, a **salt-free** or **salt-poor diet** (see Treatment of Ascites, for additional details) has been found materially to reduce the retention of fluids in the body.

In proper cases, **salt restriction** aids materially the elimination of retained sodium chloride and of water, generally causing a decrease of edema. Excessive salt restriction occasionally causes an increase or reappearance of edema, due to a loss or insufficiency of the renal function to automatically dilute and concentrate the urine, and a certain amount of water, which would ordinarily be excreted, is retained, and the edema increases accordingly. In very acute forms of nephritic edema, salt restriction should be combined with **drink restriction** so that the edema may be diminished or disappear. To test the renal capacity an occasional drinking or a salt day, singly or combined, is a useful means. This will also test the degree of retention of chlorides, or of retardation in their excretion. Persistence in salt restriction is desirable. It is useless to try it only for a few days, for so short a period

does not suffice to spare kidneys or enable them to regain their function. A week or even two weeks sometimes pass before any result is apparent, particularly in the more chronic forms of nephritis. Croftan (*Jour. Amer. Med. Assoc.*, Feb. 17, 1912).

In a case of lymphatic leukemia with edema in the left leg for 6 months and of both for 3 weeks, the writer **kept down the intake of fluids**. The output of water was increased materially by not allowing the patient more than 700 to 1100 c.c. of fluids during 24 hours, and finally not over 600 c.c. With this the urine totaled systematically from 1020 c.c. to 1500 c.c. The edema subsided and the patient was greatly relieved and able to walk again. W. Nonnenbruch (*Münch. med. Woch.*, Oct. 27, 1914).

The writers, after observing 50 cases of cardiac dropsy, systematically treated with **reduction of fluids and of salt**, state that these measures alone may restore conditions to clinically normal and that even if the case is only partly benefited, it materially re-enforces the action of the heart and kidney restoring compensation except in the absolutely doomed cases. They recall that the Karell treatment is on the same principle, but that it represents unnecessary deprivations. The writers give a light nourishing diet of 2000 calories but with only 700 or 900 Gm. of fluid and no salt in the bread. The patients do not object to this diet for a week. After this it is modified to allow 1500 or 1800 Gm. fluid and 2.5 Gm. salt with 2500 calories, but no meat. This fluid-poor and salt-poor diet is less distasteful the more pronounced the dropsy; that is, it is tolerated better, the more urgently it is needed. **Rest** is an important feature of the treatment. Tchertkoff and Heim (*Rev. Med. de la Suisse Rom.*, Sept., 1918).

ASCITES.

DEFINITION.—Accumulation of serous fluid in the peritoneal cavity, due

to, and occurring as, a symptom of diseased conditions of the peritoneum itself, such as inflammation, cancer, and tuberculosis; abdominal growths or structural enlargements pressing upon the portal veins; thrombophlebitis; obstructive disease, wounds, or rupture of the lymph- and chyle- vessels; affections of the heart, lungs, liver, and kidneys which produce either venous engorgement or altered states of the blood and consequent leakage from the vessels.

SYMPTOMS.—In moderate effusions the front of the abdomen is flat, and the flanks bulge when the patient assumes the recumbent posture. In the lateral posture the uppermost flank is depressed, while the front of the abdomen becomes prominent. When the effusion is large, the whole abdomen is distended and barrel-shaped, preserving its contour in any posture. The surface is uniformly smooth, unless there be encysted pockets of fluid. The skin is tense; lineæ albicantes may appear, and enlarged superficial veins, especially in portal obstruction, be observed. Fluctuation can be detected when a hand is placed on one flank, and tapping done on the opposite side by the other, the muscular wave being cut off by the edge of an assistant's hand placed firmly and vertically in the median line. Percussion gives dullness over the fluid and tympany over the intestines, the varying location of these signs depending upon changes in posture. Examinations should be made in the dorsal, lateral, standing, and knee-and-hand postures. Tyson has called attention to the fact that tympany in the flanks is sometimes noted even when the effusion is considerable.

In extensive ascites the upward pressure may seriously interfere with the

functions of the liver, lungs, and heart, while gastrointestinal disturbances, such as tympanites, nausea, vomiting, and constipation, are not uncommon. Albuminuria and frequent urination may occur. Ischemia is a necessary consequence of the pressure of the fluid upon the arterioles and capillaries.

DIAGNOSIS.—Catheterization eliminates a distended bladder. In hydatid, pancreatic, and ovarian cysts the fluid is at first localized at the diseased organ. Subsequently there is dullness over the center of the abdomen and tympanites in the flanks, exactly the opposite conditions to those in ascites. Pregnancy, especially with excess of amniotic fluid, may cause confusion in certain cases, but careful physical examination and the personal history can hardly fail to remove any difficulty in diagnosis. Hydronephrosis, when extensive, and when the urine contains no products from the kidney, can closely resemble encysted or even general ascites. The possibility of upward displacement of the liver and apparent enlargement in ascitic effusions should not be overlooked. Aspiration may be necessary in obscure cases in order to ascertain the nature of the fluid, or to outline the liver and spleen, enlargements of which are at times accompanied with ascites.

PATHOLOGY.—The character of the fluid varies according to the cause. It is usually of a low specific gravity (1010-1015), clear, straw-colored, and albuminous, undergoing at times spontaneous coagulation. Cancer and tuberculosis are apt to produce hemorrhagic effusions, while a milky color, though not common, may be produced by disease of the lymphatics, perforation of the thoracic duct, filariasis, or an excessive milk diet. The fluid in diffuse

septic peritonitis and the blood in ruptured tubal pregnancy possess their well-known characteristics, but are not ordinarily regarded as strictly ascitic effusions.

Study of the causes of ascites as found in 2217 autopsies which included 224 cases of ascites in which 1 quart or more of fluid was present. Cases of septic peritonitis and hemoperitoneum being omitted, the bulk of the remaining cases were due to one of five causes: Cardiac weakness (89), nephritis (26), abdominal neoplasms (44), cirrhotic liver (23), and tuberculous peritonitis (15). Adherent pericardium (9), eclampsia (3), thrombosis of vena cava, portal and mesenteric veins (3), chronic fibrous peritonitis (3), uterine fibromyoma (3), intestinal obstruction (2), pancreatitis (1), ovarian cyst (1), acute yellow atrophy of liver (1), status lymphaticus (1). The causes of ascites in 3086 cases observed clinically at the Massachusetts General Hospital (1870-1910) were: Total cases of cardiac weakness from all causes 1397, renal and cardiorenal 665, cirrhosis of liver 325, tuberculous peritonitis 263, intestinal obstruction 86, ovarian cysts and tumors 63, uterine fibroma 55, neoplastic peritonitis 53, cancer of liver and lymph-nodes 30, cancer of intestines and lymph-nodes 56, cancer of pancreas and lymph-nodes 11, malignant lymphoma (thoracic and abdominal) 5, adherent pericardium 36, pernicious anemia 15, leukemia 12, syphilis of liver, etc., 4, thrombosis of vena cava, portal, and mesenteric veins 10. R. C. Cabot (Amer. Jour. Med. Sci., Jan., 1912).

TREATMENT.—The treatment of ascites consists in the removal, if possible, of the primary cause. According to indications, appropriate measures are addressed to the heart, lungs, liver, and kidneys. At the same time diuretics and, especially, hydragogue cathartics are employed. **Elaterium**,

judiciously administered, and salines are valuable agents.

It is well to limit the drinking of fluid, and to support the patient's strength with **hematics** and **tonics**.

Case of ascites which was greatly benefited by the injection, into the peritoneal cavity, of **adrenalin** 1:1000 solution after other measures had met with but small success. The first injection consisted of 8 minims (0.5 c.c.) of the solution, which was given directly into the fluid in the abdominal cavity. In all, 9 injections were made, ranging from the smallest, 1 to 8 minims (0.6 to 0.5 c.c.), up to 2 c.cm. (30 minims). At that time the ascites had entirely disappeared, and the patient was not troubled with orthopnea. The injections were discontinued. Since then his improvement has been progressive. T. Mellor Tyson and H. D. Jump (Therap. Gaz., Jan. 15, 1911).

Should these measures fail, tapping must be done under aseptic precautions, and repeated when necessary. The puncture is usually made in the median line midway between the symphysis pubis and navel, but can be made midway between the symphysis and antero-superior spine, care being taken not to wound the intestine. The bladder should be previously emptied.

A **capillary tube**, the inner end of which is perforated laterally by many small holes for the distance of 1 cm. recommended. After the tube is introduced, the trocar is withdrawn and the tube is connected with a rubber tube and left *in situ* for several hours, the fluid draining off slowly. The method shortens the time consumed by the physician in paracentesis, and does away with the danger of collapse from the rapid reduction of intra-abdominal pressure. Buth (Deut. med. Woch., June 11, 1914).

Usually in true cirrhosis the portal vein is so tied up in adhesions that a true Eck fistula is not feasible. The

writers devised a modification of the **Eck fistula** consisting of an anastomosis of one of the large mesenteric veins with the iliac vein at the point at which they cross.

This is a more positively curative procedure than the operation advocated by Miller, which amounts to continuous tapping. Edward Martin and J. E. Sweet (Jour. Amer. Med. Assoc., Oct. 16, 1915).

Successful results have been obtained by draining ascitic fluid in chylous ascites through the opening between the fascial layers of the thigh, where the fluid is gradually absorbed.

In a boy 8 years of age with chylous ascites, the writer used the **Lambotte-Handley** plan of drainage. Six strands of No. 7 white silk 4 inches long were grasped in narrow blade forceps and thrust through the peritoneum to the outer side of the femoral vessels in the thighs and at the upper angle near the umbilicus.

Five months later examination revealed no abnormality of the abdomen and the patient was in a good state of health. F. Huber (Arch. of Pediat., xxxvii, 600, 1920).

In ascites due to portal obstruction from cirrhosis of the liver, or from compression in enlargement of that organ, **Talma's operation** (see p. 61, vol. i) should be considered, while the occasional good effects of incision and withdrawal of the fluid in tuberculosis of the peritoneum are to be borne in mind. Vidal and Martel anastomose the vena cava with the portal vein. Villard anastomoses the mesenteric vein with the ovarian. Tavernier, Talma, Morrison, and Lambotte resort to omentopexy.

Operations which promise even a very moderate amount of success are thoroughly proper in such a fatal condition as ascites due to hepatic cirrhosis; severe operations are improper because the patients are usu-

ally in very poor condition for resisting trauma; some form of **omentopexy** or of **lymphangioplasty** is much superior to mere paracentesis and is the operation of choice; where milder measures fail, drainage into the veins may be proper; but all means of direct anastomosis between the portal vein and inferior vena cava are probably unjustifiable. J. F. Binnie (Interstate Med. Jour., April, 1912).

The literature shows that about 40 per cent. have been cured of those to whom the **Talma operation** has been applied. It is not universally successful because the outcome depends on the functional capacity of the liver. Continuous autodrainage of ascites is still in its infancy, but the results already obtained are promising, especially as it requires such an insignificant operation in contrast to the laparotomy for the Talma operation. It is applicable for all forms of ascites, and the effect becomes evident at once. The drain-tube technique seems to have given the best results, but the best material for it is still a question. Fish-bladder tubes were entirely absorbed in five months in the experiments on animals; hernial sac tissue in four months. Autoplastic fascia tissue gave the best results in the experiments on animals; it heals smoothly in place, takes nourishment from the tissues and lasts a long time. A. Blad (Ugeskrift for Laeger, July 22, 1915).

Statistics show that from 35 to 50 per cent. of cases of ascites due to cirrhosis of the liver may be cured by an early **Talma operation**. Those of Ruotte, Soyesima and Miller indicate that **venoperitonostomy** is capable of yielding such favorable results that a further trial of this method is to be recommended. J. D. Heard (Jour. Amer. Med. Assoc., Oct. 16, 1915).

The fact that celiotomy in tubercular peritonitis has been found curative owing to the admission of air, i.e., of oxygen, into the peritoneal

cavity led Potain to try the use of **oxygen injections** into this cavity in tuberculous ascites, after withdrawal by puncture of the ascitic fluid. One thousand or more cubic centimeters of the gas can be injected without causing inconvenience other than temporary tympanites. It has also been found of value by Teissier in alcoholic cirrhosis.

In the treatment of tuberculous ascites by **heliotherapy**, the writer urges a reaction against the medical management of these cases that economically is often a hardship. The high sun exposure can be practised at home. Gelpke (*Corresp. blatt f. schweizer Aerzte*, Jan. 12, 1918).

Gilbert, of Geneva, having experimentally obtained satisfactory results in tuberculous pleural processes by reinjecting into the subcutaneous tissues or veins of the arm serum obtained by puncturing the pleura of the same subject, Audibert and Monges resorted to the same measure, termed **autoserotherapy** in the treatment of ascites. The method is as follows: After sterilizing the skin surface and bringing about local anesthesia with ethyl chloride, the needle of a sterile hypodermic syringe of 10 c.c. capacity is introduced into the peritoneal cavity in the left side and a little of the ascitic fluid withdrawn. An assistant exerts pressure on the abdominal parietes if required. The syringe is then drawn out until its point lies in the cellular tissues, when the contents are reinjected. Progressively larger doses of ascitic fluid are to be used (3, 5, 8, and 10 c.c.—48, 81, 130, and 162 minims). This procedure is repeated at intervals of six days and the treatment continued for two months. The

method is painless and does not cause abscesses, local reaction, or fever. The authors claim that it produces lasting polyuria, retards transudation into the peritoneum, and permits of discontinuing the milk diet.

Case of ascites of hepatic origin in which benefit was derived from re-injection of the patient's own ascitic fluid, commencing with 3 c.c. (48 minims) and never surpassing 10 c.c. (162 minims). The injections were made at intervals of about six days, and 12 injections were made in all. There was no pain, no local reaction, nor any apparent influence on the temperature or on the elimination of chlorides and urea. The main effect was a copious and persistent polyuria which brought about notable improvements in the general condition as the ascites was drained away. The writers withdrew salt from the diet, emphasizing the injurious action of ingested salt in ascites resulting from liver disease. They now apply this autoserotherapy in all cases of recurring ascites. V. Audibert and F. Monges (*Presse médicale*, Feb. 2, 1910).

In 2 cases of atrophic cirrhosis with ascites, the writers prevented reaccumulation of the fluid and greatly improved the general condition of the patient by administering, intravenously, massive injections of ascitic fluid. Every ten days or two weeks 300 to 500 Gm. (10 to 16 ounces) of fluid were removed and at once injected into one of the arm veins. Improvement was not marked until after the fifth or sixth injection. One of the patients, thus treated for four months, appears to have been cured. The other is still under treatment.

In the above cases all measures previously tried—repeated simple punctures, subcutaneous injections of ascitic fluid, diuretics, salt-free diet, etc.—had failed. The treatment was painless and led to no unpleasant effects. Sicard and Galup (*Soc. Méd.*

des Hôpitaux; Bull. méd., Feb. 18, 1911).

Undoubted case of cirrhosis, with atrophied liver, splenic enlargement, prominent collateral circulation, and positive methylene blue test, in which **autoserotherapy** and other measures led to rapid absorption of an ascitic accumulation of 6 months' standing. Subcutaneous injections of 10 c.c. (2½ drams) of ascitic fluid were continued on alternate dates. On the third day a free flow of urine set in, with the result that 11 days later the ascites had disappeared. The patient was subsequently given salt-free food, then placed on a careful chloride-containing diet, with the result that ascites and the symptoms due to portal congestion have not returned. Vitry and Sézary (*Revue de Méd.*, Feb., 1913).

Autoserotherapy has been resorted to in the most varied forms of ascites, and the only contraindication is a purulent ascitic fluid. Small subcutaneous injections should be tried first. It is the only method permissible in tuberculous ascites, and here it is advantageous to combine it with laparotomy and proteolysis. In Laënnec's cirrhosis massive intravenous injections may be successful, but they are absolutely contraindicated in tuberculous ascites as they contribute markedly to generalization of the process. Another contraindication is renal impermeability, because in such cases the toxic substances which should be contained in the urine, pass into the pleural collection. Otherwise, ascitic autotherapy appears to be a method of remarkable innocuousness. Pron, alone, has mentioned a local complication, a hard edema on the entire right side, without the redness of a lymphangitis, which lasted several days.

A **salt-poor diet** has been found beneficial in a large proportion of cases. The blood in seeking to maintain its osmotic balance absorbs what sodium chloride it can obtain from the tissues. The osmotic power of its serum being reduced, the latter

leaves the circulation with less freedom, while the renal elimination of water is facilitated.

In a series of 14 cases of tuberculous ascites seen by the writer, only 5 were slightly benefited by diuretics. An extensive trial was then made with the **salt-free diet** recommended in other forms of ascites. Normally, about 12 to 15 Gm. (3 to 4 drams) of salt are ingested, and an equal amount is excreted by the kidneys. If the patient takes only oatmeal, rice, stewed fruits, eggs, milk, and unsalted butter, the amount may easily be reduced to 2 or 3 Gm. (30 to 45 grains). The amount may safely be increased to 4 Gm. (1 dram) by allowing some meat, bread, and vegetables, all prepared with a minimum of salt. The patient stays on this diet for weeks; but occasionally a few days of normal diet should be interposed, to avoid monotony.

The results of treatment were as follows: 8 out of 10 cases lost their ascites completely after salt-free diet for from five to seven weeks. W. Alwens (*Therap. d. Gegenwart*, Mar. 30, 1910).

The **Karell diet** has served the writer best. The patient receives daily at 8 A.M., 12 M., 4 P.M., and 8 P.M. 200 c.c. (¾ pint) of raw or boiled milk, warm or cold, according to taste. No other food or liquid should be given. This meets with violent opposition from the patient, owing to thirst, which is particularly tormenting during the first 3 or 4 days. The patient can rinse out his mouth with water, but he must swallow none. Hunger, if too urgent, may be relieved by giving a small piece of dry toast or zwieback with each portion of milk. During the first few days the patient requires continual encouragement to persist with the treatment, but the moral effect of the rapid loss of weight, as shown by daily weighings, together with the very evident decrease of the edema, prove sufficient argument to him, and no further complaint is heard.

The diet may usually be increased at the end of a week's time by giving a soft-boiled egg, without salt or pepper, at 10 A.M., and a piece of zwieback at 6 P.M. The next day an egg may be given at 10 A.M. and at 2 P.M., with a piece of white bread, and from now on food is gradually increased until a full diet is being taken. During this time the daily quantum of liquid should not exceed 800 c.c., ($\frac{1}{2}$ quart) and this fluid should be in the form of milk, until the patient receives a full diet, when the milk may be discontinued and cocoa or tea substituted, the amount of liquid remaining the same, however. No more than 800 c.c. of fluid should be taken for from 2 to 3 weeks after the disappearance of ascites. During the treatment, which must be carried out with the patient in bed, the bowels must be kept open, and for this purpose laxatives in pill form are preferable to salines, merely because they require no water for their administration. Goodman (*Arch. of Internal Med.*, June, 1916).

Our Associate Editor, James M. Anders, holds that the **Karell cure**, which is much more used abroad than in America, is, in the opinion of His, not only effective in renal and cardiac dropsy, but alleviates the disturbance in breathing and other distressing symptoms not dependent upon the edema present in many of these cases. Prof. Anders deems it valuable before actual decompensation has taken place; for example, in cases of aortic valvular disease showing simply premonitory symptoms, associated perhaps with a mild grade of arteriosclerosis. After positive involvement of the kidneys and the presence of uremia it is altogether contraindicated. He does not advocate the use of the treatment in valvular disease with dropsy in which the kidneys are intact, but in all such cases there should be allowed more food of a higher caloric value, with aid to elimination by other means, such as **rest, cardiac stimulants**, etc. The use of **iron** is of advantage when administered in conjunction with the Karell cure.

CHYLOUS ASCITES.

This is a form of ascites in which true chyle, a milk-like fluid, accumulates in the peritoneal cavity.

SYMPTOMATOLOGY.—Chylous ascites cannot as yet be deemed to possess a clinical history of its own, the chylous effusion being in most instances a cause of surprise when the ascites becomes sufficiently marked to demand evacuation by puncture. The abdomen presents the signs of ordinary ascites: enlargement, intestinal tympany, ready displacement of the liquid fluctuation, and dyspnea. The skin of the abdomen is often, however, the seat of supplementary veins, and the effusion not only tends to be quantitatively very great, but it is apt to return very rapidly and again in large quantities after puncture. The fluid is characteristic: it is white, lactescent, odorless and opaque, and fails to undergo putrefaction, the fluid itself, owing to its wealth in lecithin, being probably antiseptic.

Among the symptoms observed in such cases, ascribable in almost every instance to one of the numerous causative disorders, have been the signs of peritoneal involvement, and, independently of any such complication: fever, marked adynamia, premature senility, vertigo with tendency to syncope and finally, tinnitus aurium.

DIAGNOSIS.—Chylous ascites simulates fat-cell ascites, also met with in cancer and in tuberculous and chronic peritonitis. Its identity may be established, however, by the osmic acid stain, which colors the fat-cells black. The pus of purulent peritonitis, another source of con-

fusion, is readily identified microscopically.

ETIOLOGY AND PATHOLOGY.—Though not peculiar to them, chylous ascites is met with relative frequency in children. Among the causes that have been recorded have been inflammation of the thoracic duct; rupture of some chyle canal through traumatism or excessive venous distention; cardiac disorders capable of promoting the latter; pressure of a tumor upon the duct or transudation through its wall; intestinal sarcoma; chronic, cancerous, and tuberculous peritonitis; miliary tuberculosis; impaction due to filariasis, and other entozoa.

Report of 126 cases collected from the literature, in conjunction with 10 personal cases, tabulated as to age, sex, existing abdominal conditions, treatment, and result. As to exciting cause, 24 cases of chylous ascites complicated carcinoma; 17 cases were due to tuberculosis; 11 cases accompanied cardiovascular conditions; 8 cases were due to disease of the liver; 7 cases followed puerperal sepsis; 4 cases were the result of congenital cysts. In addition there were three instances where chylous ascites followed infection with the *Filaria sanguinis hominis*. Obstruction to the thoracic duct was observed *post mortem* in 11 of the cases, and the duct or receptaculum was found to be ruptured as the result of traumatism in 7 of the cases. Sixty-one of the cases were females, 50 males, and in the remaining reports the sex was not given. A further analysis as to the number of the cases occurring at the various periods of life gave 6 under 1 year of age; 3 between 1 and 5 years; 13 between 5 and 10 years; 9 between 10 and 20 years; 12 between 20 and 30 years; 34 between 30 and 50 years, and 24 after the age of 50. L. N. Boston

(Jour. Amer. Med. Assoc., Feb. 18, 1905).

Case due to blocking of the thoracic duct high up in the thorax, leading to lymph and chyle stasis, and transudation of these fluids below. The body of the pancreas was imbedded in a large mass, $1\frac{5}{8} \times 3\frac{1}{2} \times 1\frac{3}{4}$ inches, apparently consisting of coalesced lymph-nodes of a pinkish color and granular appearance. C. B. Van Zant (Denver Med. Times, July, 1910).

The disease cannot be said to present any special morbid anatomy, apart perhaps from its differentiation into its two types: true chylous and the pseudochylous ascites.

Report of 171 cases of chylous and pseudochylous ascites, including 3 cases coming under the personal observation of the authors. Milky ascitic fluid may be recognized in two main types—chylous and pseudochylous. The milky appearance of the latter is not due to free lecithin, fat, or a mucinoid substance, but to a lecithin-globulin complex, which is held in suspension by the inorganic salts present in the fluid. By dialysis these inorganic salts may be removed, the lecithin-globulin complex precipitated, and the opalescence of the ascitic fluid disappears. The marked resistance of the fluid to putrefaction is due to the presence of lecithin. Wallis and Schollberg (Quarterly Jour. of Med., part i, iii, 301, 1910; part ii, iv, 153, 1911).

Case of pseudochylous ascites in a man of 60, admitted to the hospital with ascites, who in four months was tapped eight times, the smallest amount removed being 6 quarts, the largest 8 quarts. At the autopsy there was found a tumor at the pyloric orifice of the stomach cancerous in nature. The liver appeared perfectly normal. This showed how difficult it is in some cases to ascribe the disease to cirrhosis of the liver. The distinction between chylous and pseudochylous effusions is that the milky appearance of the latter is due,

as in this case, to a combination of serum-globulin with lecithin or other lipid material. The remarkable resistance to putrefaction displayed by pseudo-chylous effusions was due to lecithin, as proved by the fact that on the abstraction of the lecithin they rapidly decomposed. Senator's view that the presence of sugar is indicative of the chylous nature of an effusion is found untenable. In the case reported the ascites was not explained by autopsy, there being no demonstrable obstruction of the portal circulation or alteration of the peritoneum, the chief lesion being a cancer of the pylorus. (See also page 189 for the nature of the pseudo-chylous fluid.) F. P. Henry (Med. Record, June 17, 1911).

PROGNOSIS.—According to the researches of Wallis and Schollberg based on 171 cases, the prognosis is grave, the mortality reaching 66 per cent. in chylous ascites and 70.4 per cent. in the pseudo-chylous form.

In 1900 Shaw collected a series of 115 reported cases, of which 71 were chylous and 33 chyliform, the remaining 11 being doubtful. That it is a very serious condition is borne out by his mortality statistics, which report that of the 115 cases 5 cases were relieved and 14 cured. How this cure was brought about was not stated. The mortality as derived from this series is noticeably very high, the average duration of life after the onset of the ascites being five and one-half months. Report of personal case cured by Route's operation. G. W. Morse (Boston Med. and Surg. Jour., Feb. 22, 1912).

TREATMENT.—This reduces itself to the elimination, if possible, of the cause and to symptomatic measures. **Tapping** is indicated, as it is in ordinary ascites. **Celiotomy**, especially if the case be due to tubercular peritonitis, may prove curative by admitting air, *i.e.*, oxygen, into the

peritoneal cavity. The insufflation of **oxygen** through the cannula used for tapping might also prove advantageous in cases traceable to the same cause. In suitable cases **Route's operation**, vein transplantation, has proven curative.

Route, in 1901, reported a novel operation for the relief of ascites which was successful in 2 out of 3 cases. More operations of this kind may have been done, but a rather hasty review of the literature reveals no further attempts. Patterson, in 1910, described an operation for the same purpose in which he used a glass button or spool between the peritoneal cavity and the subcutaneous tissues. He sums up his result in the following statement: "I have performed this operation in several cases of ascites secondary to malignant disease; also in cases of cirrhosis of the liver, with marked diminution of the abdominal distention and to the great relief of the patients."

The writer, in a personal case, operated as follows:—

Sept. 6, 1911: Operation. Ether anesthesia. Dorsal position. Right saphenous vein isolated and freed downward for 6 inches from saphenous opening. Branches tied and cut. Distal end ligated in two places and cut between. Skin incision extended to median line of abdomen below umbilicus, and peritoneum opened at this point. About 1 inch to right of median line a stab wound was made through the peritoneum and the end of the vein drawn through. Protruding end of vein split and the two flaps turned back and sutured with fine silk. Vein proved patent by probe. Peritoneum closed and skin closed over vein, which lay imbedded without kink or pressure in fat. Light spica bandage. Patient stood operation well and was in good condition. Ascitic fluid only partially evacuated.

Sept. 17: Patient sitting up.

Sept. 21: Fluid in abdomen has returned and patient prepared for similar operation on left side.

Operation: Internal saphenous vein dissected out from saphenous opening to knee, tied and cut at distal end. Vein covered with gauze wet with hot salt solution, and left muscle-splitting incision made in lower left rectus. Trapdoor flap of peritoneum turned back, and end of vein pulled through stab wound at its center and end split. The two flaps of the split end of the vein were then sutured back to the peritoneum with vaselin silk, using fine straight needles. Digital examination through the small incision revealed only "hosepipe" intestines, which were so firm and stiff that any exploration of the abdominal cavity was impossible. The surface of the bowel was much whiter than normal, but the peritoneal coat was lustrous and smooth. Wound then closed as before. After operation the transplanted vein was apparently dilated and patent.

Patient recovered well from the operation, but by Oct. 1 the fluid has returned to considerable extent and 8 quarts were withdrawn by tap. The left transplanted vein was apparently still patent, however, and the left leg became much swollen, but not red nor tender.

Oct. 7: Patient up and about ward feeling well and with no evidence of return of ascites. No fluid demonstrable in chest or abdomen.

Oct. 13: Discharged relieved and left hospital.

Subsequent history: Patient resumed his work in a shoe factory in September, 1910, and has been perfectly well ever since. G. W. Morse (Boston Med. and Surg. Jour., Feb. 22, 1912).

ANGIONEUROTIC EDEMA.

DEFINITION.—An affection marked by transient circumscribed edematous swellings; closely resembling, if not identical with, giant urticaria; probably due to abnormal vasomotor influences, and frequently associated with more or less gastrointestinal disorder.

SYMPTOMS.—The onset is sudden, and usually affects the hands, feet, genitalia, and the face, although the lips, tongue, or glottis may be involved. Periodicity in the attacks has been noted. Redness, heat, itching, or urticaria may precede the attack. Vomiting, colic, and pain are common digestive symptoms, while hemoglobinuria and cardialgia have been observed, as well as affinities with Raynaud's disease and certain forms of severe purpura. Osler refers to a case with swelling of the whole arm.

Blue edema is a form of angioneurotic edema first described and named by Charcot in 1889. It occurs usually in association with hysterical forms of paralysis, and is characterized by suddenness of onset and local lowering of temperature, which may even precede its appearance. The edema generally affects only a single limb, and it is always situated at its extremity. Its duration is variable—sometimes it persists for several years, sometimes it occurs periodically, and sometimes it can be made to disappear and reappear at will by hypnotism. Most authors agree that there is vascular spasm.

Case of hysterical edema in a woman aged 21 years who showed no hereditary antecedents, and in whom three years and a half after the loss of a sister and other troubles there developed a loss of voice, with changes in her character, mental depression, insomnia, loss of appetite, and incapacity to work. She lost 20 pounds in a few weeks. After a period of improvement in which the aphonia still persisted, pain developed in left knee with the appearance of a painful, purple, ecchymotic spot, making walking difficult. This soon disappeared. In July there appeared a

similar spot on the back of the left wrist, with swelling of the articulation. The swelling and pain extended to the forearm and then to the hand. Contracture of fingers and wrist followed. A cast was applied under chloroform. The contracture lessened spontaneously during the patient's unconsciousness, and she spoke in a loud voice. Six weeks later the removal of the cast showed the swelling but slightly diminished and the fingers still contracted; since then the swelling has increased with febrile state in the evening, rising after the daily application of the cast. Temperature, pain, and touch normal; loss of smell, slight contraction of visual field. Plantar reflexes lessened on both sides, knee-jerk normal, pharyngeal abolished, conjunctival and abdominal present.

Examination by radiography showed the osseous system normal, even the hand, elbow, and forearm. The left forearm was bent at a right angle, the wrist half-bent and twisted toward the inside, hand half-closed, fingers flexed on the palm and greatly swollen. Skin of hand and lower part of arm white and drawn; there was hardly a dent under pressure. Part of the edematous surface gave the sensation of heat. The swelling stopped abruptly in the upper part of the lower arm; between this and on the lower part was plainly discernible a red line. The fingers and wrist were permanently contracted. Movement painful, although those of the elbow were easily made. Slight atrophy of left arm. Patient complained of constant pains in wrist, fingers, and hand. Hard pressure on swollen parts painful. In spite of electric and galvanic baths, application of collodion and methylene blue, and removal of bandages there was no change in the patient's condition. Glorieux (*Jour. de Neurol.*, Feb. 20, 1911).

ETIOLOGY.—Heredity is in some cases a marked predisposing cause.

Emotional disturbances and cold may be influential. The immediate cause is supposed to be a dilatation of the blood-vessels, with transudation of serum. From the nature of the disease an underlying toxemia is not improbable.

[Harbitz (*Münch. med. Woch.*, Nov. 14-28, 1911) writes of "Fatal Familial Angioneurotic Edema," and cites a fatal case in which there was edema of the face and throat. A father and one grandfather died from the same affection, and other members of the family suffered. There are 170 cases on record, 36 dying from edema of the larynx. The disease may take the form of effusion into a joint. It is thought that anaphylaxis to some unknown substance is operative. There may be recurrent affections due to slight, almost imperceptible, edema. W. S. GORDON.]

The family whose history of 64 individuals from the first to the fifth generation traced back to 1 case, included 28 cases of angioneurotic edema and 15 deaths from an acute form of the disease. The cases were about equally divided between males and females. J. R. and T. R. Crowder (*Arch. of Internal Med.*, Dec., 1917).

Excellent results were obtained from **adrenalin**, giving 4 minims (0.25 c.c.) of the 1:1000 solution. When given in the first stage of numbness and itching the injection would abort the attack at once. Later the writer gave **adrenal gland**, 3 times a day. The attacks were diminished in frequency and severity, then ceased. J. A. Codd (*Brit. Med. Jour.*, June 16, 1917).

Paroxysmal Form.—Another type of angioneurotic edema of hysterical origin is characterized by the repeated occurrence of transitory edema affecting geometrical or segmented areas of the cutaneous surface. It is sometimes associated with disturbances of sensation quite hysterical in type.

Several cases personally witnessed in which the features of a subcuta-

neous edema of fairly sudden onset occurred, the whole area becoming affected uniformly at the same time; the surface of the skin was generally natural in color, but in some instances was hyperemic or white and cold or purplish; the edema at its height was firm and non-pitting; later during subsidence it became softer; the edge was always abrupt. There was no pain, only a mechanical inconvenience, and the duration was usually from eight hours to two days. The areas correspond to the natural divisions of the body, *e.g.*, the mammal, or with areas covered by articles of clothing, stockings, socks, gloves, etc., that is, with the areas called "geometrical" or segmental by writers on hysterical phenomena. There were some sensory disturbances. This condition must be differentiated from the hysterical chronic edema of Sydenham and Charcot and the angioneurotic edema described by Milton, Quincke, and Osler. But by careful attention to the "geometrical" type of the area affected, the abrupt edge, the disturbances in sensation, lack of gastrointestinal crises, or the presence of other visceral manifestations, cases of paroxysmal edema should be divided into two categories—those of Quincke's edema (angioneurotic edema) and those of hysterical origin. F. H. Edgeworth (Quarterly Jour. of Med., ii, p. 2135, 1909).

Two cases of *persistent hereditary edema of the legs (Milroy's disease)* with acute exacerbations were observed by the writer. Hope and French have summarized the characteristic findings as follows: Restriction of edema entirely to the legs; absence of any traceable cause, general or local; strong family predisposition; painlessness of the pale swollen legs (apart from the "acute attacks"); absence of constitutional symptoms; sharpness of limitation of the upper level of the edema; incidence in both sexes; permanence of the edema. No treatment seems effective, though the swelling may be

held in check by **bandaging**. The disease does not shorten life. J. Phillips (Cleveland Med. Jour., May, 1914).

In a case described by the writer the hard edema covered the entire front of the trunk and neck like a sleeveless sweater, with 2 patches on the cheeks. The entire right side, besides, showed anesthesia. The patient was a soldier of 40, invalided home. The man had a history of measles, malaria and cholera. The edema developed almost all at once and shows a tendency to a blue tint, suggesting Charcot's *œdème bleu des hystériques*. It is symmetrical and is accompanied by hemianesthesia, lateral hemianopsia and other nervous disturbances, including recurring aphonia. Carnelli (Policlinico, Med. Sect., 1918).

PROGNOSIS.—The disease is often obstinate, being apt to recur at intervals of several weeks, but life is not endangered unless the larynx be involved.

TREATMENT.—Especial attention should be directed to the gastrointestinal tract; general hygienic rules should be enforced, and tonics administered when required. Coincident disorders should be rectified. Osler calls attention to the value of large doses of **strychnine** and the prolonged use of **nitroglycerin**. The disease often proves refractory to treatment.

The writer obtained favorable effects in 3 cases from desiccated **thyroid gland** $\frac{1}{2}$ grain (0.03 Gm.) three times a day increased to four doses daily. Dryland (The Medical Press, Aug. 8, 1917).

EDEMA NEONATORUM.

This rare condition, more or less general, and observed in the first few days or weeks of life, occurs in weak infants. The swelling is usually confined to the lower portions of the body, and the lower limbs. Weakness of the right heart is supposed to be one of the

main causes. The differentiation from sclerema, as given by Fairbanks, is as follows: "In edema the skin is usually soft; it may or may not pit; it can be pinched up in folds unless the edema is extreme; rigidity of the body is not present; the skin, when cut at autopsy, exudes serum, and when examined under the microscope large spaces are seen where the connective tissue has been forced apart by the fluid. In sclerema the skin is hard, in severe cases as if frozen; it never pits; it cannot be pinched up, but seems as if it were fastened down to the underlying parts; there is more or less rigidity of the entire body; there is no exudation of serum when the skin is cut, and when examined in section it and the subcutaneous tissue are seen as a dense mass in which fibrous tissue predominates and no dilated interconnective-tissue spaces are present. The only way in which the two affections are similar is that they both occur in feeble and often premature infants in the first few days of life."

Reference has been made to the causes of the above-mentioned edemas. Anemia, marasmus, heredity, toxemias, nervous influences, cold, and other factors are supposed to be more or less operative, but the exact etiology, as applied to certain groups of cases, is not yet determined. Toxemia, with reflex nervous influences upon the vasomotor function, is probably responsible for a large number of the cases, and Fischer's theory, in this connection, should be borne in mind.

The treatment is governed by the symptoms and the general indications.

IDIOPATHIC OR ESSENTIAL DROPSIES OF CHILDHOOD.

The characteristic feature of this condition is the appearance of edema

in one or more parts of the body without albuminuria or sedimentary evidence of organic disease of the kidneys: without clinical or postmortem evidence of organic disease of the heart or kidneys. It may occur in children of any age, but is not limited to childhood. It occurs in children who previous to and during its presence are otherwise well; or it occurs, accompanied by symptoms more or less peculiar to it, in children previously and subsequently well; or, finally, it occurs immediately preceding, accompanying, or immediately succeeding some disease other than the organic conditions above mentioned.

Increase or decrease of sodium chloride in the diet has quite an influence on edema. In nephritis or lost cardiac compensation in the adult, edema can be produced and intensified by increasing the sodium chloride in the diet, and then diminished by a reduction of the same. Infants without heart or kidney lesions react similarly, especially where disturbances of nutrition are present. It is impossible to accomplish this in older children with normal heart and kidneys. It is essential, however, that some abnormal conditions be present to obtain the effects—usually some disturbances of general nutrition. F. Hamburger (*Münch. med. Woch.*, Bd. lviii, S. 2500, 1912).

The series of coincident symptoms of the second class is only collectively, not individually, peculiar to the affection. The disorder may be acute, subacute, or chronic. It cannot, therefore, be said, in any given case, that the edema is positively primary or definitely secondary. The time of year seems to have an influence upon its occurrence only in so far as the seasons are accompanied by those factors that are of undoubted importance in the etiology, such as extremes of temperature, espe-

cially cold, or the prevalence of gastrointestinal derangements, with their accompanying toxemias and conditions of low vitality. In 25 per cent. of the cases anemia was present; in 43 per cent., gastric or enteric disturbance, usually diarrhea; in 15 per cent., marked emaciation; in 15 per cent., subnormal temperature; in about 7 per cent., urticaria, and in 4 per cent., purpura. The temperature was normal in a few cases. Symptoms pointing to edema of the larynx or throat occurred in 5 per cent. In 2 cases of supposed meningitis the symptoms may have been due to cerebral edema. The most common abnormal associated feature was gastrointestinal disorder (Fairbanks).

[Under this heading can be mentioned the cases reported by R. H. Edgeworth (Lancet, July 22, 1911). The patients were 6 children, of healthy parentage, who developed subcutaneous edema in from one to sixteen weeks after birth. One case, with facial involvement, recovered; 5 died in from one to sixteen weeks. In at least 3 no albumin was found in the urine, and in 2 cases no post-mortem evidence of nephritis could be discovered. All had more or less of diarrhea. In one case calcium chloride lessened the edema. Toxins acting upon capillary vessels defective from birth were supposed to be the cause of the edema.

W. E. Hume (British Medical Journal, Sept. 2, 1911) discusses "General Edema Following Gastroenteritis in Children." He describes a group of cases occurring in 1908, and following gastroenteritis. There were no evidences of heart or kidney lesions. Salt metabolism was the same as in healthy children. In 2 cases there was an abnormal degree of fibrosis in the medulla of the suprarenal gland. The vascular condition was improved by the injection of epinephrin, improvement being more rapid with than without this substance. The author thinks that the edema may be due to the influence of gastrointestinal toxins upon the suprarenal

medulla. There might be an absence of suprarenal secretion. Or, the toxins may act directly upon the cells of the capillary vessels.

Again: P. Nobécourt and Paiseau (Bulletin de la Société de Pédiatrie, Paris, June, 1911) mention the case of a 2-month infant who lost weight, developed dropsy, and died in less than a month. The parents were healthy, and the child was breast-fed. All the organs appeared sound. The autopsy revealed only fatty degeneration of the liver. W. S. GORDON.]

During an epidemic of gastroenteritis among the babies, 13 cases of edema made their appearance in eleven days. The patients all had gastroenteric trouble either immediately preceding or at the onset of the edema. The symptoms were as follows: Face pale, pasty-looking, apathetic, depressed; temperature subnormal; skin dry, soft, deeply pitting on pressure. In a number of the cases the edema was intense, and would rapidly change from the face to the legs or other parts of the body and *vice versa*. The weight increased before or with the appearance of the edema and decreased when the edema subsided. The urine in 9 cases contained albumin, but the casts were very few or none. One case which died while the edema was present showed normal kidneys at autopsy, so the kidney trouble was evidently not primary. The children were in three different wards on different floors, attended by different nurses; yet, the trouble broke out simultaneously. All the patients were artificially fed. De Wolf (Medical News, Feb. 21, 1903).

In the Manchester Children's Hospital, during the autumn, it is fairly common to find infants who have edema of the feet and hands. The edema usually appears toward the end of an attack of gastrointestinal catarrh, when the vomiting and diarrhea are getting better. It does not develop during the acute stage. The edema is bilateral and attacks the dorsum of the hands and feet, and occasionally the face becomes puffy,

giving the appearance of a renal condition. The heart and lungs are usually found normal. The urine is high-colored, acid, and foul-smelling, and contains a few leucocytes, but no blood or casts. Small amounts of albumin are found at times, but, while there is no nephritis, there is renal inadequacy and the child is suffering from toxemia. Necropsy shows no change in the kidneys, except slight cloudy swelling in the tubules. The blood in these cases shows a high proportion of hemoglobin and a slight increase in the number of red blood-cells. The circulation is not especially feeble. Edema, when it occurs in the course of gastrointestinal diseases, is a serious symptom, although quite a large number of cases recover. Hugh Ashby (Practitioner, May, 1911).

The affection is supposed by the majority of observers to be of nervous origin. The cases of intermittent hydrops of the joints are probably due to the same cause. Certain cases of ascites occurring in young girls and unaccompanied with marked general disturbance, except, in one or two instances, transient fever, vomiting, and loss of appetite, have been reported. In 4 of the 6 cases mentioned by Quincke the condition disappeared with the onset of the menses.

TREATMENT.—Besides treatment of the underlying conditions, the measures indicated in this disease should include a diet in which the **proteids** are liberally represented, mainly to enhance vascular tone. Of the diuretics **potassium citrate**, with small doses of **digitalis**, have given the best results. Morphine is not only useful to prevent the abdominal symptoms which are often severe, but also to diminish the effusion. **Mercury biniodide** in small doses or the **iodides** are indicated when a his-

tory of syphilis, inherited or acquired, can be traced.

The prognosis is usually good in the essential edema of children, edema of the larynx being the only cause of death. Abdominal symptoms are often severe. **Morphine** seems to be the only agent that helps. **Scarification** and application of **supra-renal extract** to the edematous parts is recommended in edema of the larynx. Tracheotomy may be necessary. Avoidance of predisposing articles of diet and relief of constipation are prophylactic measures. Schwarz (Amer. Jour. of Obstet., Oct., 1908).

Five cases of edema and anasarca in infants cured by **specific treatment**. In one case there was a clear history of inherited syphilis. In another the edema was traceable to a liver affection, and in another to septicemia. The other cases demonstrate that edema and anasarca are liable to result merely from gastrointestinal disturbances, even when it is apparently mild. The anasarca of digestive origin is the result of well-defined lesions in the organs involved, for which the gastrointestinal affection is primarily responsible. Lereboullet (Annales de méd. et chir. infantiles, Feb., 1909).

[E. Favel (Correspondenz-Blatt für schweizer Aertze, Basel, August 10, 1911) describes a method for **subcutaneous drainage** in ascites. He uses a glass spool, with broad ends and a caliber of 1 cm., one end of which is worked into the peritoneal cavity. A hole to support the other end is made in the subcutaneous tissue. Not even local anesthesia is necessary. The omentum should be kept out of the lumen. W. S. GORDON.]

When there is edema of the larynx scarification with **epinephrin solution** applied locally to cause contraction of the edematous tissues is necessary to prevent asphyxia. The bowels should be kept free by means of **saline laxatives**. As in other

forms of edema, a **salt-poor diet** is also of material prophylactic value.

In infants who are the subjects of acute or chronic disturbances of nutrition excess of salt may cause edema, even when there is no evidence of disease of the kidneys or heart, and the writer records a case of similar nature in a boy 5 years of age. The child suffered from chronic digestive disturbance and neurasthenia. He was of emaciated and miserable appearance and was sent for a "cure" to Carlsbad, where he improved considerably. Shortly after his return he was brought to the author, who found general edema and marked swelling of the prepuce. The urine was free from albumin, and on examination a faint and variable systolic murmur was heard, which had often been observed before and was not regarded as indicative of any cardiac lesion. On inquiring into the diet taken by the child it was found that the broth which the child had been given was very salt, and that it had caused considerable thirst. A **diet poor in salt** was ordered, and in three days the edema had lessened considerably, the child having lost $2\frac{1}{4}$ kg. in weight during that time. The child is now completely sound and in good health. Franz Hamburger (Münch. med. Woch., Nov. 21, 1911).

In 1908 the writer had 4 cases under his care in the children's ward of the Royal Victoria Infirmary at the same time (*vide supra*). From the facts that the vascular conditions were improved by the injection of **epinephrin**, that the children improved more rapidly under its administration than without it, and that in these 2 cases there was an abnormal degree of fibrosis in the medulla of the suprarenal gland, the writer suggests that attention in future be paid to these glands when opportunities of examining them occur. Hume (Brit. Med. Jour., Sept. 2, 1911).

WM. S. GORDON,
Richmond, Va.

ASPHYXIA. See RESUSCITATION.

ASPIDIUM (U. S. P.), or **MALE FERN**, is the rhizome of the *Dryopteris filix-mas* found in Europe, America, Asia, and some parts of Africa, and the *Dryopteris marginalis* indigenous to North America. Aspidium contains, among other more or less active constituents: *filicic acid* (a volatile oil), *aspidin*, *aspidinin*, *albaspidin*, and *filmaron*, to which the therapeutic properties of the drug are ascribed.

The value of the oleoresin of male fern depends on the presence of aspidin, as well as that of filicic acid. Out of 11 preparations examined, 6 contained aspidin in large proportion (2 to 3 per cent.), while filicic acid was absent; 4 contained filicic acid, but no aspidin, and 1 contained small quantities of both. These results show that a high content of aspidin excludes the presence of filicic acid, and *vice versa*. An oleoresin containing principally aspidin is decidedly preferable to one rich in filicic acid. Boehm (Südd. Apoth. Zeit.; Bull. of Pharmacy, vol. xxi, No. 11).

The main drawbacks of male fern are its varying strength, disagreeable taste, and irritating properties manifesting themselves in vomiting and intoxication. The principles occurring in male fern were carefully tested by the writer. He found that all the active properties were contained in the amorphous acid *filmaron*, which constitutes about 5 per cent. of the extract. Filicic acid and *albaspidin* are also anthelmintic, but to a less extent, and are also less abundant in the extract. The average dose of *filmaron* is 0.7 Gm., and patients very rarely experience other after-effects besides slight nausea or transient abdominal cramps. In efficacy it seems to be almost equal to the fresh extract from the rhizome. A. Jaquet (Therap. Monats., Aug., 1904).

PREPARATIONS AND DOSE.—

The official preparation of aspidium is the oleoresin: *oleoresina aspidii*, a thickish, brown fluid having a bitter, disagreeable and even nauseous taste. The dose is from 15 to 45 grains (1 to 3 Gm.). This may be administered in capsules previously dipped in a solution of formaldehyde or coated with keratin, or in pills dipped in salol to render them insoluble in the gastric juice and prevent irritation of the stomach. It may also be given in emulsion,—the form in which it is generally used for children. Formulas for emulsions are given below, under Therapeutics. Aspidium should never be administered with castor oil; filicic acid being soluble in the latter, toxic phenomena may result.

A dangerous combination recently, a prescription calling for the following ingredients, was presented to an eastern pharmacist for dispensing:—

R *Oleoresin of male fern* 1 dr. (4 Gm.).
Oil of turpentine .30 grs. (2 Gm.).
Castor oil 2 oz. (60 Gm.).

M. Sig.: Take at one dose.

The presence of castor oil in the above mixture would cause the prescription to be a dangerous one, since the filicic acid, one of the poisonous constituents of male fern, is dissolved by the castor oil, its absorption being thus promoted. The oleoresin of male fern should never be prescribed with castor oil or other oily substances; in some European countries there is a legal prohibition against dispensing extract of male fern in combination with castor oil. F. J. Wulling (*Journal-Lancet*, Jan. 15, 1911).

PHYSIOLOGICAL ACTION.—

Aspidium is toxic to all entozoa, and is probably the most reliable agent at our disposal to destroy any of the varieties of *tenia*, or tapeworm,

Study of the physiological action of male fern by means of the "demarkation current" of DuBois-Raymond, which occurs when one end of the muscle is suspended in a solution of the drug to be tested. It was found that, of the different principles and their derivatives, phloroglucin, filicinic and butyric acids were inactive; of the remainder, the filicinic acid butylamin was least active, then followed aspidinol, flavaspidic acid, albaspidin, and finally filicic acid as most potent. For protozoa the order of toxicity was somewhat different: thus,—albaspidin, filicic acid, flavaspidic acid. A number of other invertebrates were tested, from cœlenterata to crustaceæ, and in all, with the exception of certain echinodermata, the great virulence of male fern was demonstrated. Its active principles proved to be strongly poisonous for all kinds of organized plasma, but more particularly for muscle-tissue. This was most beautifully shown in the case of worms, and the empirical use of male fern as an anthelmintic finds its scientific proof in these experiments. W. Straub (*Archiv f. Exper. Pathol. u. Pharmacol.*, Bd. xlviii, S. 10, 1902).

Aspidium is a powerful irritant of the gastrointestinal canal, and its use in excessive doses gives rise to toxic phenomena, even though its absorption is slow. Fortunately, doses sufficient to destroy the parasite are harmless to the patient—unless administered with oil—and are readily eliminated from the intestine. The action of aspidium on the spinal cord has been compared by Cushny to that of strychnine, since toxic doses cause a distinct increase of reflex excitability. The dominant symptoms, according to Prévost and Binet, are paralysis and rigidity of different muscles, including those of the heart and intestines. Paralysis of the heart

is the usual cause of death, the organ being found after death in a condition of firm contraction and non-irritable. Peristalsis is almost entirely suppressed in the rabbit, cat, guinea-pig, and pigeon.

In experiments performed by Georgiewsky, animals poisoned acutely with large doses failed to show post-mortem changes capable of accounting for death. Animals poisoned gradually, however, showed marked blood-changes: diminution in the number of erythrocytes and the proportion of hemoglobin, even though the animals had lost considerable serum through numerous alvine discharges, thus increasing the viscosity of the blood. Though the tissues in general were normal, the liver and kidneys were found to contain considerable iron, doubtless originating from the broken-down red corpuscles—the cause of jaundice in cases of poisoning.

[Acute poisoning is accounted for, from my viewpoint, by reflex constriction of the arterioles through the sympathetic system, and the resulting blocking of the tissue circulation thereby. The muscular rigidity would then be a result of the accumulation of toxic wastes which follows deficient circulation of arterial blood in any organ. The hemolysis of slow poisoning corresponds with that awakened by many agents which promote the formation of antibodies which, produced in excess, destroy not only the antigen (the aspidium in this instance), but also the blood elements. C. E. DE M. S.]

ASPIDIUM POISONING.—Text-books of pharmacology lay but little stress upon the dangers of poisoning by aspidium, but men who are in the practical field speak otherwise. Grawitz, for example, has emphasized these dangers. Nausea, faintness, tremors, drowsiness, tinnitus aurium,

lassitude, and icterus are not uncommon, while vomiting, profuse sweating, purging, severe abdominal pain, diminished urinary flow with albumin and hyaline casts, twitching of the muscles, tetany, delirium, coma, and death have not infrequently occurred as a result of excessive doses. In a series of 78 reported cases of aspidium intoxication studied by Sidler-Huguenin (*Correspondenzblatt für schweizer Aerzte*, Nov. 17, 1898). 12 terminated fatally. In the cases saved nervous disorders may follow.

Case in a man of 38 who took 8 Gm. (2 drams) of extract of male fern with 16 Gm. (4 drams) of castor oil, the combination being a proprietary mixture (Tritol-Stark), to expel a tapeworm. The man believed that he had the parasite and took the medicine without consulting a physician. The drug caused vomiting, violent clonic and tonic cramps, irritation of the kidneys, and fever, but the eyes did not seem to be affected. The tendency to circulatory disturbances was seriously aggravated, the toes were congested and numb, and there were blue patches on the leg. The man had to stay in bed for six weeks with varying degrees of pain in the leg, and he was left with serious paresis of the limb, the type suggesting poliomyelitic paralysis. Magnus-Levy (*Berl. klin. Woch.*, March 27, 1911).

Optic atrophy, with typical gray or white discoloration of the optic nerve and contraction of the retinal arteries, has been observed after severe intoxications, while transient amaurosis and amblyopia, with dilated non-reacting pupils, are comparatively frequent. In 44 out of Huguenin's 78 cases temporary or permanent disease of the optic nerve was the main lesion. A suggestive fact in this con-

nection is that castor oil had been given along with the extract in 57 per cent. of the cases.

Case of a woman aged 35 who thirteen years before had been treated with extract of male fern for tapeworm, with success. Portions of *Tania mediocanellata* being found again in her stools, her own medical attendant ordered her extract of male fern 8 Gm. (2 drams), calomel 0.8 Gm. (12.3 grs.), divided into 16 doses, placed in capsules, 2 of which (= 15.4 and 1.5 grs.) were to be taken every ten minutes. After one and a half hours from the beginning of the treatment, she passed an entire tapeworm, but shortly afterward she experienced general sensations of weakness, and was attacked by typical tetanic spasms. These spasms could be stopped by firm pressure on the large vessels and nerves of the arm. Trousseau's and Chvostek's phenomena were well marked. Recovery was complete in three weeks. No signs pointing to involvement of any organ could be detected during the course of the tetany. Treatment consisted of warm baths and hot packs to the extremities. Dammer (Münch. med. Woch., Nov. 13, 1900).

Case found in deep coma which had been preceded for two days by headache, vertigo, apathy, and complete anorexia. The diagnosis at first sight seemed to rest between epilepsy and apoplexy. A hasty examination showed a rapid, regular, but thready pulse, wide pupils, increased patellar reflexes, and a tonic spasm of the entire body, especially of the arms. The rapid reaction on stimulation made it more and more likely that the case was one of intoxication. It was then found that the patient had swallowed about 2½ drams (10 Gm.) of pure extract of male fern for an alleged tapeworm. W. Gotthilf (Münch. med. Woch., Bd. xlviii, S. 1096, 1901).

Case of a man aged 52 years who took 12 capsules of ethereal extract of male fern. He got rid of the tape-

worm, but an hour later fainted. All attempts to bring him to proving fruitless, the patient was given lemon juice. He immediately rallied, vomited, and rapidly improved. A slight syncope having occurred an hour and a half later, the same treatment, followed by a second evacuation, effected a complete cure. Anonymous (Medical Bulletin, Nov., 1907).

TREATMENT OF ASPIDIUM POISONING.—As a light case of poisoning frequently develops into a serious one, the use of aspidium should be discontinued when any untoward sign appears: headache, nausea, twitchings, etc. Aspidium being slowly absorbed, a purgative is indicated, but castor oil should be avoided, as it would aggravate the case. Citrate of magnesia, by causing watery stools, will best clear the intestinal canal of what amount of the drug it may contain. Hypodermic injections of ether, camphor, aromatic spirit of ammonia, with hot coffee by mouth or rectum, or other stimulants, and hot (108° F.) saline solution enteroclysis, are indicated.

THERAPEUTICS.—Aspidium is now used exclusively as a remedy for tapeworm and *Ankylostoma duodenale*. Special care is necessary, and the dose administered should be especially small in young, anemic, and badly nourished subjects. Intestinal, renal, and cardiac diseases also enhance the liability to toxic effects. Chronic alcoholism, chronic appendicitis, and lactation are also contraindications. Castor oil should not be used either before, during, or after the administration of aspidium.

There are various methods of using the drug. Most authors favor a preliminary purgative and the withholding of food some time before

administering the vermifuge. Ewald, however, holds that this practice favors absorption of the drug and facilitates the production of toxic effects. He resorts to no preliminary treatment except, perhaps, a mild saline aperient, followed by coffee, and the dose of the extract used by him never exceeded 30 grains (2 Gm.). One hundred cases treated in this manner proved entirely successful, and failed to show the least untoward effect. Boas also ignores the preliminary measures and uses smaller doses than are usually recommended.

The writer's method is as follows: He gives, fifteen minutes after a breakfast of coffee with zwieback, the following formula, which has acted well in his hands: Fresh ethereal extract of male fern, 2 or 2½ drams (8 to 10 Gm.); powdered jalap, 7½ grains (0.5 Gm.); simple syrup, enough to make 1 ounce (30 c.c.). This mixture should be well shaken. The parasite usually appears in three to four hours. The writer considers it unnecessary that the teniafuge should be taken fasting, but if evacuation of the bowels does not take place or is delayed he advises the employment of an enema of about a quart of warm water. A laxative is then administered on the following day. Schilling (Therap. Monats., Bd. xxii, S. 187, 1908).

Yet, the impression prevails, and probably on correct premises, that where there is no preliminary abstinence from ordinary food the parasite is protected by the latter, and the remedy fails to produce its toxic effect upon it. It is customary, therefore, to keep the patient on a light diet a couple of days, and if constipation prevails to administer a purgative. The oleoresin is then administered in capsules, 5 or 6 grains (0.3

to 0.39 c.c.) in each, giving 1 capsule every ten minutes until the total amount to be administered—30 or 45 grains (2 to 3 Gm.)—has been given. One hour after the last dose, a bottle of citrate of magnesia is administered, and the patient is instructed to defecate in a vessel containing water, so as to prevent breaking up the parasite. Where this procedure does not succeed, it is because mucus in large quantities protects the worm; the use of Carlsbad salt before resuming the treatment is then indicated.

Male fern at present is not always helpful in this country because of the lack of care in collecting the rhizome and in preparing an active ethereal extract. This, however, is a condition which doubtless would soon be remedied if once considerable demand existed for an active extract. Schultz (Jour. Amer. Med. Assoc., Sept. 30, 1911).

When the parasite is passed, search for the head should be made in a shallow receptacle, using the microscope to identify it.

The following plan, originally described by the late Dr. Leslie Ogilvie, was found to answer in every case in which the writer tried it: For three days previous to the administration of the male fern the patient is kept entirely on a liquid diet; a pint and a half of milk and a like quantity of beef tea answer very well. To promote a free action of the bowels and to favor the removal of mucus, the following is given:—

℞ *Sodii bicarbonatis* gr. xx (1.3 Gm.).
Sodii sulphatis . . . ʒj (4 Gm.).
Spiritus chloroformi ℥xx (1.25 c.c.).
Aq. menthae pip-eritæ . . q. s. ad fʒj (30 c.c.).

Take three times a day.

On the night before the male fern is given the patient should have the following draught:—

℞ *Magnesii sulphatis* ʒss (15 Gm.).
Tinct. jalapæ fʒj (4 c.c.).
Tinct. chloroformi comp. .. ʒxx (1.25 c.c.).
Aquæ q. s. ad fʒiss (45 c.c.).

This is repeated next morning at 7 o'clock if the previous dose has not operated. At 8 A.M. male fern is given in a mixture:—

℞ *Extracti filicis fluidi* fʒj (4 c.c.).
Pulv. tragacanth. comp. gr. xx (1.3 Gm.).
Spiritus chloroformi ʒx (0.6 c.c.).
Aq. menthæ piperitæ .. q. s. ad fʒj (30 c.c.).

At 9 A.M. this dose should be repeated. At 11 A.M. a purgative is given, and if the bowels do not act promptly an enema of a pint and a half or 2 pints of soapy water administered. The movements should be carefully examined to find the head, and if the above treatment has been faithfully carried out it may be sought for with confidence. It is desirable to keep the patient in bed for two or three hours after the bowels have acted, as the male fern may cause faintness. F. de H. Hall (Clinical Journal, Aug. 6, 1908).

When capsules or pills cannot be used, the oleoresin may be given in the following way:—

℞ *Oleoresinæ aspidii*,
Tinct. vanillæ āā ʒxxx (1.8 c.c.).
Pulv. acaciæ ʒss (2 Gm.).
Aq. destill. fʒj (30 c.c.).

This is taken in one dose, the directions given above as to preparation and subsequent purgation being carefully followed.

As a remedy in **hookworm infection**, aspidium has frequently been used. Bruns treated 21,612 cases with it and found that it expelled all the parasites in 98.5 per cent. of cases, though in 15 to 30 per cent. it was necessary to give a second dose and 4 cases of blindness occurred in

the series. Ashford and King in Porto Rico found that in a certain proportion of cases ethereal extract of male fern could be used successfully where thymol had failed. The drug seemed to vary considerably in activity, however, and, because of the large doses necessary, greater nausea, dizziness, and prostration were complained of by the patients than followed the use of thymol. The dose of the oleoresin required in hookworm disease is 75 to 150 grains (5 to 10 Gm.), given in 2 doses one hour apart (Dock and Bass).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
 Philadelphia.

ASPIDOSPERMA. See QUEBRACHO.

ASPIRATION. See PARACENTESIS.

ASPIRIN, or ACETYLSALICYLIC ACID, is the acetyl derivative of salicylic acid [$\text{CH}_3\text{COO.C}_6\text{H}_4\text{COOH}$]. It occurs in the form of small, colorless crystals, which have a distinctly acid, but not unpleasant taste. It is soluble in water in the proportion of 1 to 100, and readily in alcohol and ether.

DOSE AND MODES OF ADMINISTRATION.—The dose of acetylsalicylic acid is from 5 to 15 grains (0.33 to 1 Gm.). It should not be administered with alkalis, as these will split up the drug into acetic acid and salicylic acid, and induce the gastric discomfort which the latter acid causes in its pure state. It may be given in capsules, wafers, or in a solution with sugar or syrup and water, but the most prompt action is obtained by placing the powder upon

the tongue and washing it down with a little water, or by giving it in gelatin capsules.

The writer has observed that when aspirin and sodium bicarbonate are brought together, either in solution or in dry form, the aspirin suffers a partial decomposition with the liberation of acetic acid. The solution soon acquires an acid taste and develops the peculiar acetic acid odor, while the pulverulent mixture becomes at first moist, then cakes, and in a few days forms a semifluid mass. Rousseau (*Pharm. Zeit.*; *Phila. Med. Jour.*, March 14, 1903).

The potassium salt of aspirin which, water free, contains about 90 per cent. of aspirin and 10 per cent. of potassium, is soluble. It is a white powder, easily soluble in water. To increase this solubility 0.15 Gm. (2½ grains) starch is added to each tablet, which contains 0.5 Gm. (7½ grains) soluble aspirin. Görges (*Deut. med. Woch.*, June 27, 1912).

As quinine is combined with aspirin very frequently in the treatment of influenza, severe colds, and muscular rheumatism, this matter, according to an editorial writer (*Therap. Gaz.*, Sept., 1916), attains a position of first importance.

There does not seem to be any doubt that under certain conditions, which are as yet unexplained, the mixing together of aspirin and quinine results in the production of toxic manifestations. Indeed, it has been claimed that death has resulted from such a combination, and if a mixture of quinine and aspirin was the cause of death it behooves druggists to be cautious in dispensing this combination. Scoville (*Jour. Amer. Pharm. Assoc.*, May, 1915) showed that decomposition of a mixture of quinine sulphate and aspirin sometimes takes place and a poisonous product is formed, to which the term quinotoxin has been applied.

PHYSIOLOGICAL ACTION.—

The physiological action of aspirin resembles that of salicylic acid (*q.v.*), but the untoward effects on the stomach produced by the former are

relatively slight, as salicylic acid is not split off from it until it reaches the alkaline media of the intestine. Nor does it have as marked a tendency to produce depressing effects on the heart as the ordinary salicylates exhibit in corresponding doses. This is probably due, however, merely to its slower absorption. Nor does it cause tinnitus or sweating quite as readily. Anorexia, so common when the ordinary salicylates are used, is altogether obviated. It is believed by some to produce its effects by causing contraction of smooth muscles.

The author found that aspirin was decomposed not only in the gastric, pancreatic, and intestinal juices, but also in the saliva, and even in water. In a personal case of poisoning, absorption must have taken place from the stomach, because the symptoms came on so quickly after ingestion. The amount of salicylic acid in the molecule of aspirin is small, and it is probably the peculiar union of this acid with acetic that renders its effect so toxic in these cases. Borri (*Gaz. degli Ospedali*, Sept. 13, 1903).

Series of experiments with dogs in which the writer found that the lethal dose was about ½ grain (0.032 Gm.) to each 2 pounds of body weight. Large doses caused temporary lowering of the arterial tension and slowing of the pulse; the heart sounds remained regular, except when the dose exceeded the therapeutic limit, nor was there any change in temperature or the respirations. Aspirin exercises a decided contracting action upon smooth muscle, especially that of the uterus, whether gravid or non-gravid, the effect being noted from fifteen to thirty minutes after administration of the drug. Chidichimo (*Ann. di ost. e gin.*; *Zentralbl. f. Gyn.*, No. 40, 1906).

Aspirin is largely used as a substitute for the salicylates; when pure it has no action on the stomach, and is decomposed in the intestine into

salicylates and acetates. The compressed tablets frequently contain some free salicylic acid, produced by contact with water during manipulation. Haynes (*Folia Therap.*, vol. iii, p. 13, 1909).

Many cases were encountered during the epidemic of influenza in which severe stomach disturbances followed the use of acetylsalicylic acid or sodium salicylate, sometimes with actual hematemesis. The drug was taken in the usual doses and intervals, and the disturbances began gradually and grew constantly worse, with sometimes sudden hematemesis; or melena was the first indication of the gastric hemorrhage. It was very severe in some of them, occurring with syncope, and returning in 1 case after only 3 or 4 tablets had been taken. Sodium salicylate was responsible in only 2 of the cases. Luis y Yagüe (*Arch. Espanoles de Enf. del Ap. Digest.*, Nov., 1918).

ASPIRIN POISONING.—The most evident toxic effect of this drug, either in an oversensitive subject or after large doses, is edema of the face, especially about the eyes, nose, and mouth. The pharynx and larynx may also be involved, exposing the patient to death from edematous laryngitis. The lips and eyelids are usually congested and everted, and there may be severe headache and tinnitus. There may be great dyspnea, difficulty of deglutition, and marked rapidity of the pulse, with cyanosis involving the entire body. An eruption, urticarial or erythematous, may occur after these symptoms or appear alone, as in a case witnessed by Elverson.

Case of aspirin poisoning in a woman aged 50 years who took 100 grains (6.48 Gm.), the drug being given in 10-grain (0.65 Gm.) doses every three hours, with marked toxic effects. All the sensory nerves were affected, numbness and anesthesia resulting, followed by pain. The heart

was not affected at all, but the drug had a marked diuretic action lasting some days. There was also an acute inflammation of the right middle ear, due entirely to the drug. Dockray (*Brit. Med. Jour.*, Dec. 30, 1905).

Case in which $7\frac{1}{2}$ grains (0.5 Gm.) of aspirin, every thirty minutes, eight times, caused considerable general cyanosis, with cold extremities. The heart's action was 70 and very weak, intermitting every third or fourth beat. The skin was rather harsh and dry. The mind was perfectly clear. There was some nausea, with vomiting at intervals. The writer removed the stomach contents at once by means of **stomach-tube**; the stomach washings consisted merely of some mucous and biliary coloring matter. He applied **external heat** to the back and extremities, and gave **strychnine**, gr. $\frac{1}{30}$ (0.0022 Gm.) hypodermically. The patient began to rally after two hours, and recovered. Cooper (*W. Va. Med. Jour.*, June, 1910).

Case in which two doses of 5 grains (0.32 Gm.) each taken at an hour's interval brought on marked aspirin intoxication, including edema of the face, congestion of eyelids and lips, dyspnea, difficult articulation, etc. These symptoms, probably due to idiosyncrasy, disappeared in about three days. Graham (*Jour. Amer. Med. Assoc.*, Jan. 28, 1911).

The writer observed a patient who, after taking a capsule containing 5 grains (0.5 Gm.) of aspirin was taken with vomiting in about half an hour, followed by a "stiffness" in the throat making him think he was developing a tonsillitis. An hour and a half after taking the capsule his face was swollen and cyanotic, the eyelids were edematous and almost closed and the conjunctiva injected, the whole face swollen, the breathing was labored and asthmatic, the nasal mucosa gorged, preventing nasal breathing, the buccal mucosa and pharynx were dark red and swollen, the uvula twice its normal size. The pulse was 120, soft and full, temperature 98. The breathing was such as one might

expect with edema of the glottis. No treatment was instituted; the symptoms largely disappeared in 6 hours, but there was a fine, papular rash on the trunk the next morning. The patient reported a similar experience about a year before, lasting about 5 hours, after taking a capsule of $2\frac{1}{2}$ grains (0.16 Gm.) each of aspirin and phenacetin. E. N. Reed (Jour. Amer. Med. Assoc., Mar. 7, 1914).

The writer mentions 17 cases from the literature, and reports 3 seen personally, in which the use of acetylsalicylic acid was followed by edema, the lids and face swelling, the skin puffing up sometimes down as far as the chest. In some of the cases there was also a tendency to urticaria, near the swollen patches or more diffuse. In some of the cases the edema involved the mucosa of the nose and pharynx; in 2 cases there was edema of the larynx. The edema rapidly reached its height and subsided as a rule in 24 hours.

The doses administered had ranged from 0.3 to 1 Gm. (5 to 15 grains), and the pathologic reaction occurred always at the first dose, independent of the amount taken. In 2 of the cases the drug was continued without further mishap. A. Klercker (Hygiea, lxxviii, No. 4, 1916).

A case of **chronic aspirinism** was observed by the writer in a woman, aged 50, suffering from rheumatoid arthritis. She took 10 grains (0.6 Gm.) of aspirin twice daily for 7 years. During the first 6 years of the treatment she exhibited no sign of poisoning, nor of gastrointestinal irritation nor of cardiac or mental depression. The first untoward sign was an intractable simple conjunctivitis, the patient complaining of "sand in the eyes." There was a well marked hyperemia of both the palpebral and ocular conjunctiva; there was a slight degree of chemosis and considerable lachrimation. A week later an urticaria appeared which was not relieved by either dietetic or the usual local or internal remedies. In a few days the patient was entirely

covered by a typical urticaria major, the rash, assuming in parts the characters of an acute circumscribed edema, and elsewhere a severe urticaria bullosa. The patient was weak from insomnia, had diarrhea and vomiting. Massive edema of the tongue and fauces, causing marked dysphagia, an urgent tracheotomy being only averted by a prolonged administration of ice and ice water combined with astringent gargles. Vision was obstructed by an extreme palpebral edema. The urine gave an intense bluish violet reaction when tested with liquor ferri perchloridi, but the exact percentage of salicyluric acid was not estimated. A diagnosis of chronic aspirinism was made, and the drug rigidly withheld.

Medicinal treatment consisted of 5 grains (0.3 Gm.) of ichthyol and a mixture containing liquor arsenicalis, tincture of belladonna and calcium lactate, 3 times a day. Bromides were administered in large doses every night. At the end of the seventh week all trace of the urticaria had vanished and the urine was again normal. Moreover, since the onset of the urticaria, although all aspirin had been discontinued, all traces of the rheumatism beyond the bony deformities, had disappeared. W. F. Stiell (Pract., Sept., 1917).

Case of a man who had a chronic periostitis and osteitis of one tibia who having found that a tablet of aspirin, 5 grains (0.3 Gm.), gave him distinct relief, he continued to take the drug. At first one or two 5-grain (0.3 Gm.) tablets sufficed to keep him comfortable one whole day, but soon the patient had to increase the dose. For the past 2 years he has been taking from 5 to 12 tablets of the drug daily. The only abnormal features were obstinate constipation, slight digestive disturbances, and a rather low blood-pressure. Macht (Med. Rec., Nov. 2, 1918).

TREATMENT OF ASPIRIN POISONING.—The immediate withdrawal of the drug is, as a rule, fol-

lowed by gradual convalescence. As the morbid condition is probably due to arterial spasm, **hypodermoclysis**, to fill out the vessels, dilute the drug, and promote diuresis, is indicated. The absorption of a large dose being very slow,—fifty hours, according to the experiments of Foeckinger,—a purgative should be given to insure the evacuation of what the intestine may contain. Threatening edema of the larynx demands scarification of this organ followed by the **local application** of a 1:5000 solution of **adrenalin**, to insure contraction of the laryngeal tissues.

The toxicology of aspirin has not been studied sufficiently to warrant any conclusion as to the drugs indicated to antagonize the effects of the poison. As shown above, the toxic phenomena it provokes differ markedly from those caused by the ordinary salicylates or even salicylic acid. The fact referred to by Chidichimo, that the drug causes contraction of smooth muscle-fibers, suggests that the edema, eruption, cyanosis, etc., are manifestations of vascular spasm, and that vasodilators, comprising **amyl nitrite** inhalations, **nitroglycerin** injections, or in mild cases **sweet spirit of niter**, should be tried. **Heat** to the surface is a valuable adjunct. **Strychnine** hypodermically is indicated when there is prostration.

THERAPEUTICS. — Acetylsalicylic acid is mainly used in **rheumatism** in its various forms, **articular** and **muscular**, and even in “**growing pains**.” Given in 10- to 15- grain (0.66 to 1 Gm.) doses every four hours, the temperature, if high, usually falls to normal about the third day, when the dose may be gradually reduced until 5 grains (0.33

Gm.) are given at the same intervals. This should be persisted in three or four weeks; otherwise, a relapse is apt to occur. Its efficiency is quite as marked in children, in doses adjusted to the age. Acetylsalicylic acid seems to possess greater antipyretic power than any of the salicylates, even 4-grain (0.25 Gm.) doses exerting such an effect in **typhoid fever** (Bondi).

In 3 personal cases of acute **articular rheumatism** there was albuminuria, with casts, renal epithelia, and red blood-corpuscles in the urine. These patients had been taking other salicyl preparations, and in a few days after aspirin was substituted for them the urine was wholly free from albumin. E. Grawitz (Deut. Aërztzeitung, March 15, 1900).

The writer has given aspirin in 15-grain (1 Gm.) doses in **neuralgic affections**, especially those of the jaw. Usually in a half-hour the pain is lessened, and in an hour entirely disappears. In severe **sciatica** it has proved very efficient, being given in the same dose in connection with a saline cathartic. The pain returned at the end of twelve hours, but with lessened intensity. The aspirin is always best given upon an empty stomach and should be followed with some simple acid in several ounces of water. F. Tribold (Wiener klin. Rundschau, Sept. 9, 1900).

During the past nine years, the writer has prescribed this drug more than a thousand times for various ills, more especially all kinds of acute and chronic **rheumatic ailments**. It has always proven to be well borne by the stomach. While some authors have recorded peculiar forms of intoxication, as well as exanthemata, due to aspirin, the writer has not as yet in an extensive use of the drug met with any such unpleasant symptoms. This is possibly due to the fact that in patients whose vascular system appeared weak he always added to each dose 10 cg. (1½ grains) of powdered ergot. These good results

were not obtained by avoiding large doses; on the contrary, the writer prescribes this drug in 1-gram (15 grain) doses, to be taken every second or third hour, as deemed necessary by the urgency of the disease. E. Klaveness (St. Paul Med. Jour., Aug., 1910).

The writer gives patients suffering with **typhoid** of moderate severity 3 grains (0.2 Gm.) of aspirin as an antipyretic, repeated every four hours; where there is little sign of action the dose is increased to 4 or 5 grains (0.26 to 0.32 Gm.). According to the author, the drug should never be administered in tablet form, but dissolved in water containing a little sodium bicarbonate, which increases its solubility. The use of heat to facilitate its solution in water tends to decompose the drug. Chambers (Brit. Med. Jour., Jan. 20, 1912).

[Aspirin should never be given to lower the temperature unless it be hyperpyrexia, i.e., when the temperature exceeds 105° F. C. E. DE M. S.]

Some authors claim equal merits for it in the treatment of **acute gout**; it is certainly of value in the treatment of **migraine** which frequently attends the gouty diathesis, **sciatica**, **neuralgia**, and most varieties of **headache**.

In acute **gouty** cases aspirin should be given in the afternoon, at hourly intervals, in doses of 15 grains (1 Gm.) four to five times, but not in alkaline mineral waters, which may produce a certain amount of decomposition. S. Merkel (Münch. med. Woch., Nu. 9, 1902).

It has been found very efficient in the treatment of **chorea**, even severe attacks being subdued in a short time. The patient should be carefully watched, however, lest cardiac depression occur. Acetylsalicylic acid will sometimes abort an attack of **acute coryza**, even the form which frequently initiates **influenza**, and is useful in **cough**.

The writer has had good effects in the treatment of **cough** with aspirin. He has seen it give relief when codeine had failed. He believes that it does more than give relief,—that it tends to cure and materially shorten the duration of the cough. Ebstein (Deut. med. Woch., Bd. xxxvii, S. 1476, 1911).

Aspirin has also been used with success in **dysmenorrhea**, especially when morphine is for any reason contraindicated, as well as to control bleeding in **metrorrhagia** and **labor pains**.

In **labor** aspirin relieves pain without diminishing uterine contraction. In 276 gynecological cases the writer obtained the best results in **inoperable carcinoma**, **dysmenorrhea**, and disease of adnexa; also using aspirin as a means of relief in **painful uterine contraction** after operation. He gives 7 grains (0.45 Gm.) every half-hour up to 4 doses; 15 grains (1 Gm.) are given at a dose in cancer cases. Unpleasant symptoms were observed if upward of 45 grains (3 Gm.) were given. Goth (Gyegyaozat; Zentralbl. f. Gynäk., Nu. 38, 1904).

As noted by Dilluberger clinically, aspirin acts well in ovarian **dysmenorrhea**, since it not only diminishes the general nervousness, but also lessens the ovarian hyperesthesia. In uterine dysmenorrhea, with functional nervous disorders which have no organic basis, it acts as a strong analgesic. In severe diseases of the adnexa and **chronic metritis**, the drug lessens the intensity of the dysmenorrhea. If one administers aspirin shortly before menstruation the dysmenorrhea will be suppressed. Aspirin has a beneficial influence upon **amenorrhea** and **menorrhagia**. The writer himself found that aspirin slowed uterine contractions and exercised an analgesic effect. It is not excreted in the milk of nursing women. It causes diminution of pain in the genital apparatus, whatever be its cause. The usual dosage is 10 to 15 grains

(0.65 to 1 Gm.) two or three times daily. F. Chidichimo (Therap. Monats., Nu. 8, S. 389, 1906).

In **asthma** of the bronchial type, aspirin has been found to lessen the violence of the attack and to curtail its duration. It is said to relieve the fulgurant pains of **tabes dorsalis** and the gnawing pains of **gastric cancer** and of **inoperable cancer** elsewhere.

Aspirin tried as an analgesic in a number of cases of **inoperable carcinoma** with very satisfactory results. The writer gave 1 Gm. (15 grains) two or three times daily. In the beginning the effect was often sufficient to enable the patients to do without any other anodyne for a considerable period. When its effect was not sufficient to completely dispel the pains, its further use enabled him to limit the number of morphine injections necessary for relief to one daily. Breuss (Deut. med. Zeitung, Bd. xxiv, Nu. 56, 1903).

The writer found aspirin useful in the management of **inoperable carcinoma**; 7 to 15 grains (0.45 to 1 Gm.) relieve the pain in severe cases, and often permit sleep. In some cases in which morphine was not well borne the aspirin was quite as efficient in overcoming the pain. Ruhemann (Deut. med. Woch., June 2, 1904).

Aspirin should be avoided where there is cardiac weakness, or where, in acute disorders such as influenza or scarlatina, the stage of depression has been reached. It has been recommended in acute infections, but its tendency to depress the heart imposes a certain amount of caution in its use in such cases. The recent epidemic (1918) of influenza also showed that it tended to cause gastric hemorrhage in that disease.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,

Philadelphia.

ASTEATOSIS, or XEROSIS,

—This is a disorder of the skin characterized by abnormal dryness, which, if the condition be at all severe, is accompanied by desquamation, induration, cracking, and sometimes thickening. It is due to scantiness or absence of the sebaceous secretion, and sometimes also of sweat. It may be caused by the action of substances, such as strong alkaline fluids, which absorb these secretory products from the cutaneous tissues, or may occur in association with or as a sequela of certain skin affections, such as ichthyosis, eczema, exfoliative dermatitis, etc. It is often met with in aged subjects owing to the deficient activity of all functions, including those of the skin, and is always observed in cases of true cretinism or myxedema owing to deficient metabolism in and nutrition of the skin, including its glandular elements.

TREATMENT.—The treatment of asteatosis resolves itself into the elimination of the cause and the application to the skin of oleaginous substances, **vaselin**, **cold cream**, etc., at regular intervals.

In cases of myxedema or cretinism, the usual treatment: **thyroid gland** in 1 to 3 grains (0.065 Gm. to 0.19 Gm.), doses according to the age, three times daily, benefits the asteatosis along with the malady itself. Thyroid in small doses (1 gr.—0.065 Gm.) night and morning might also be tried in senile asteatosis where the subject does not show evidences of arteriosclerosis. S.

ASTHMA.—DEFINITION.—A neurosis characterized by more or less severe paroxysmal dyspnea, due to spasmodic narrowing of the bronchial lumen, alternating with spasm of the muscles of the thorax.

SYMPTOMS.—In what has been termed "true asthma," *i.e.*, the typical form of this disease, premonitory symptoms—such as uneasiness about the chest, pallor, or a feeling of exultation, due to unusual good health—occasionally warn the patient that an attack is impending. A dyspneic

laugh, repeated sneezing, stridulous laryngitis, dyspepsia, and copious urination have been observed as prodromata of a paroxysm. Or, it may be preceded by depressive mental states, moroseness, irritability, drowsiness, headache, and vertigo.

Suddenly, in the early hours of the morning in the vast majority of cases that occur in adults—children not being as markedly prone to this nocturnal type—great constriction of the chest and more or less marked suffocation, referred to the sternal region, are experienced.

The dyspnea, in bad cases, almost reaches the stage of apnea; the respiration is wheezing in the milder cases, but in the others it is scarcely audible. The suffering of such cases is intense; the patient assumes various positions calculated to assist respiration; there is prominence of the eyeballs, distention of the superficial vessels of the neck, blueness of the lips; the skin is clammy and covered with sweat, etc.

Differentiation of the various forms of asthma may be made according to Minervini, by the attitude of the patient during the attack. In *bronchial* asthma the patient rises to reach the window for air, retaining his sense of direction and co-ordination. If he can seize the back of a chair with both hands he clings to it, his shoulders raised and his body stooping forward. In *cardiac* asthma the patient is much weaker during an attack. He sinks into a chair or sits on the side of his bed, immovable, dumb, anxious, supporting himself with his hands on the seat of the chair or bed beside him. In *uremic* asthma the patient also assumes this position from lack of energy to rise, but he is much agitated and tosses his arms and legs about, the convulsive agitation sometimes passing into a rapidly fatal depression.

The number of respirations per minute is usually reduced and the

expirations are very much prolonged. The chest remains expanded, barrel-shaped, owing to the patient's inability to contract it and expel the air; the abdomen is inordinately protruded through the descent of the diaphragm, and its muscles are tense and hard. Percussion gives rise to a drum-like, somewhat high-pitched note over the areas of the chest in which the distention of the alveoli by the imprisoned air is most marked. The cardiac and hepatic dullness outline becomes narrow and occasionally suppressed by the overlying inflated lung.

Auscultation reveals sibilous rhonchi of varying pitch and intensity, following the rhythm of the respiration. They resemble the chirping of birds of different varieties and size, simultaneously heard. This is accompanied or followed by mucous râles.

The variations in the pitch of the notes heard are due to the variations in the diameter of lumina left in the bronchi. Mucous râles are present, absent, coarse, or fine according to the nature of the secretions present. Sometimes nothing but the sibilous rhonchi are heard.

The pulse is usually slow and weak and the temperature is normal in the majority of cases, rarely reaching 100° F. Frequently it descends to 97½° F.

After a period varying from half an hour to several hours the symptoms abate and end by a more or less profuse expectoration of viscid, stringy mucous, varying in opacity according to the severity of the attack.

In a small proportion of cases the fever, cough, and purulent nature of

the sputum tend to show that catarrhal bronchitis is present as a complication. It is in these cases that emphysema is most likely to occur later on. Pulmonary tuberculosis may also occur concomitantly with bronchial asthma.

Five cases in which there was a combination of bronchial asthma and pulmonary tuberculosis. Neither affection seems to influence the course of the other except that the asthma may subside and disappear as the tuberculous process becomes installed in the lungs. In one of his cases the asthma of twenty years' standing subsided entirely after the onset of the tuberculosis. I. Hedenius (Upsal a Läkareförenings Förhandlingar, xvi, No. 3, 1910).

The writer holds that asthma is not always a diffuse process but often limited to a small area in one lung. Although the signs may be localized the symptoms may be localized or general. Whether primarily or secondarily infected the first evidence of pulmonary tuberculosis is an enlargement of the bronchial glands. Their enlargement is a part of the normal mechanism for the battle against the disease. It is through their functioning that antibodies are manufactured. When the subject is enjoying good health the glands are not interpreted as a tubercular focus; it is only when he is below normal that they are considered as of potential or possibly actual danger. P. H. Pierson (Calif. State Jour. of Med., June, 1918).

The expectorated substance is found to contain minute angular, octahedral crystals, visible with medium-power lenses, and recognized as the Charcot-Leyden crystals. They are soluble in warm water, the alkalis, and the mineral acids. These properties, as shown by Salkowski, are those of mucin. The association is further supported by the fact that Loewy found the same crystals in the

gelatinous nasal polypus, although asthma was not present.

The sputum also contains Curschmann's spirals, which are frequently sufficiently large to be recognized with the naked eye. They consist of a fine, closely packed layer of epithelial cells arranged in a spiral form around a longitudinal canal-like film. They are usually found in the thickest portions of the sputum. These are not pathognomonic of asthma, being also found in the diseases characterized by exudative inflammation of the bronchioles, as shown by Vierordt.

Large lymphoid bodies and granules, the eosinophile cells of Ehrlich, are also found, the latter sometimes in sufficient quantities to constitute a true eosinophilia.

In 150 cases studied, 123 differential blood smears showed a relatively constant eosinophilia averaging about 5 per cent., but there has appeared no significant difference between the eosinophilia in cases of extrinsic from that in cases of intrinsic asthma, nor any significant difference in the counts made during and between the asthmatic attacks in either divisions. Rackemann (Boston Med. and Surg. Jour., June 6, 1918).

The urine is generally very copious, of low specific gravity, and light colored. It is usually more toxic after a night attack.

The most important complication of asthma is emphysema. This is due to the repeated narrowing of the bronchi, which, assisted by the resulting local congestion, becomes more or less permanent and causes dilatation of the alveoli.

The pulmonary circulation is interfered with, and dilatation of the heart and edema may occur. The confor-

mation of the patient's frame becomes changed, owing to modified action of the muscles of the back and chest. The sufferer stoops and his shoulders become raised.

In recent years a certain proportion of cases have been attributed to anaphylaxis caused by one of many substances, protein, pollen, etc. to which the sufferer may be sensitive. These cases are thought to present clinical peculiarities.

Clinical peculiarities of asthma which indicate the occurrence of anaphylaxis: The intoxication which provokes the attack may be very slight; the attack has often a certain specificity; asthmatics are hypersensitized; the attack consists essentially of a dyspnea beginning with slow breathing and due to a spasm of the bronchial muscles; the attack is often accompanied by catarrh of the bronchi while that of hay fever is an integral part of an oculonasal catarrh, these troubles being due to a vasodilator and vasosecretory reflex; at the beginning or end of the attack asthmatics frequently vomit; an alternation of attacks of urticaria and asthma is common; eosinophilia is the characteristic cytologic finding of the sputum and has also been shown to exist at necropsy in the walls and in the lumen of the bronchi; the attack disappears as suddenly as it appeared; certain drugs have a favorable influence on asthma. M. J. Galup (*Gaz. des hôp.*, Mar. 14, 1914).

Patients who are extremely sensitive to the pollen of ragweed may or may not be sensitive to the proteins from other parts of the plant, and the pollen, rather than any other part of the plant, must be used for testing and desensitizing purposes; also the pollen is the only part of the plant which causes hay fever and asthma. Patients who are sensitive to corn pollen and its proteins may or may not be sensitive to the proteins of corn seed, and pa-

tients who are sensitive to the proteins of corn seed may or may not be sensitive to the proteins of corn pollen. The skin test appears to be a means of separating very closely related proteins, when such means as chemical and physical properties fail to do so. Walker and Adkinson (*Jour. Med. Research*, Nov., 1917).

The presence of the specific sensitiveness (see also Etiology) may be determined by the skin test described below.

The asthma skin test for anaphylaxis is performed as follows: A linear scarification is made about $\frac{1}{2}$ inch long, and only deep enough to penetrate the outer layers of the skin, care being taken not to draw the blood. In each case an extra scarification is made as a control, because it is a well-established fact that the mechanical injury to the skin may result in a pseudo-reaction (an elevated white area surrounded by small roseola), especially in patients with an "exudative diathesis." The scarifications are then inoculated by placing the materials to be tested (preferably in fresh solution) on the scarifications, and watching them for 20 minutes. A positive reaction appears in from 10 to 20 minutes, and in rare instances a delayed reaction is seen in 1 to 2 hours. A positive reaction gives an urticarial wheal with an irregular outline surrounded by a pink blush, both of these phenomena being absent in the control. In some cases the blush, without the urticarial wheal, is so pronounced that there is no question that there is a positive reaction. Itching may or may not be present. The reaction usually disappears within $\frac{1}{2}$ to 2 hours. The more delicate the skin the more sensitive it is to foreign protein, and the more readily will it react when it is unbroken or only slightly broken. Talbot (*Boston Med. and Surg. Jour.*, Aug. 10, 1916).

In a series of 400 cases of bronchial asthma, 191, or 48 per cent., proved sensitive to some protein. These patients had their first attack

of asthma at each period of years with the exception that after the age of 45 there was a great decrease and after the age of 60 there were only 3 cases. The number of persons who developed asthma under the age of 2 and between the ages of 2 and 5 was as great as at any other age. Four-fifths of the patients who began to have asthma during infancy were sensitive; also $\frac{2}{3}$ who began during childhood; also $\frac{1}{2}$ of those beginning asthma during young adult life; also $\frac{1}{4}$ of those beginning asthma during adult life, and none were sensitive that began asthma after the age of 50. As the age of onset of asthma increases, the frequency of sensitization decreases. More patients were sensitive to the protein of *Staphylococcus pyogenes-aureus* than to any other type of bacterial protein. Of the 11 patients who became sensitive to proteins after the age of 40, 4 were bakers and were sensitive to wheat protein, 1 was a hostler and was sensitive to horse dandruff protein, and another who was a sifter of green coffee beans was sensitive to green coffee protein; 78 patients were sensitive to the protein derived from animal hair, 68 patients were sensitive to food proteins, 92 patients were sensitive to pollens. I. C. Walker (Can. Med. Assoc. Jour., Feb., 1919).

DIAGNOSIS.—Laryngeal and Tracheal Disorders.—Attacks resembling those of the typical form may be induced by pressure on the trachea, aneurisms, goiter ("thy-mic asthma"), foreign bodies, vertebral disease, glandular enlargement, growths of the larynx and of the infraglottic space.

The tracheal traction test in the recognition of asthmatic lung is described by Abrams as follows: When the head is thrown forcibly backward the normal resonance obtained by percussion over the manubrium and contiguous lung-tissue is converted into a dull or flat sound. The findings are positive in health and in all cardiopulmonary affections, but it is ab-

sent in cases of idiopathic asthma. The test is a valuable aid in the diagnosis of idiopathic asthma, and differentiates it from symptomatic asthma and other spasmodic pulmonary affections. The tracheal traction causes a contraction of the bronchial muscle by stimulation of the pneumogastric nerves. In asthma the tone of the bronchial muscle is so reduced that it no longer responds to vagus stimulation when the neck is forcibly extended; hence, the tracheal traction test in idiopathic asthma is negative.

Asthmatic paroxysms may also be due to irregularity of the bronchial circulation through cardiac disorders, tuberculosis, bronchitis, or narrowing of the respiratory area by mediastinal tumors. As I showed in 1895, infraglottic disorders, growths, and syphilis especially may give rise to a form of dyspnea simulating that of asthma. Macintyre has also noticed that the great majority of urgent cases of acute stenosis can be seen low down in the larynx, either in the region of true or false vocal cords or below the glottis.

In croup and other laryngeal diseases there is also interference with the respiration, but it is with the inspiration and not with expiration.

Bronchitis.—In children asthma sometimes assumes the character of capillary bronchitis. In all forms of bronchitis there are absence of periodicity, greater amount of expectoration, marked increase in number of respirations, free chest motion, and more or less fever.

Pneumonia.—In this disease the respirations are greatly increased in number, and there is panting, besides free chest motion. There is also high fever.

Emphysema.—In emphysema the dyspnea is continuous, though liable to exacerbations. The dyspnea of

emphysema is often attributed to asthma. While, according to Schech, bronchial asthma of nasal origin occurs when the patient is at rest, and especially at night, the dyspnea of emphysema mostly appears on exertion.

Guha.—This epidemic disease, noted and described by our naval surgeons in Guam, has many of the symptoms of bronchial asthma. It attacks chiefly children and infants, there is marked fever, and it assumes more the character of bronchial catarrh.

Guha, which simulates asthma, is, according to McCullough, characterized by hemorrhagic infarction of the lungs, intestinal ulceration, cloudy swelling of the parenchymatous organs, and enlargements of the mesenteric and mediastinal lymph-nodes. The initial symptoms occur either in the lungs (pneumonic type) or intestinal tract (enteric type). In the primarily pneumonic type the enteric symptoms never become the more prominent, and *vice versa*. The course of the pneumonic type is sharply defined from bronchial asthma in the following respects: 1. The number of respirations is considerably increased. 2. There is continued fever. 3. The amount of expansion is not so disproportionate to the respiratory movements. 4. Inspiration is not so short and quick, and expiration is not so prolonged. 5. The percussion note has not the same hyper-resonant quality. 6. Paroxysms subside gradually, never suddenly.

Heart Disease.—Dyspnea usually follows exercise or becomes greatly aggravated by it in cardiac disorders. In advanced cases the dyspnea is continuous and the cardiac lesions are easily recognized. As Merklen observed, cardiac asthma occurs suddenly at night, on account of the greater tendency to venous stasis, with dyspnea lasting at most a half-hour. The attacks generally reap-

pear night after night, rarely twice in one night. They occur in cases of mitral insufficiency with loss of compensation, and in cases of advanced arteriosclerosis with cardiac dilatation, myocarditis, and renal insufficiency.

In 2 cases aortic aneurism was mistaken for asthma. The significant features were the suprasternal recession and stridor indicative of obstruction in or around the larynx or trachea, but incompatible with asthma. Cohen (*Interstate Med. Jour.*, Jan., 1912).

Spasm of the Diaphragm.—In this symptom there are sudden spasmodic expulsive efforts, frequently accompanied by hiccough.

Renal Disease and Uremia.—The presence of renal disease may be determined by examination of the urine, which should always be practised whenever dyspnea occurs as a prominent symptom. The dyspnea occurring as a symptom of uremia is more or less continuous and accompanied by presence of casts in the urine.

Kelp has reported a case in which attacks of asthma alternated with hallucinations, weakness of will and intelligence, followed by depression, distress and ideas of being poisoned. As the mental condition returned to normal, the asthma recurred. Norman has also reported 7 cases in which a tendency to asthma coexisted or alternated with periods of mental impairment. In only 1 of the 7 the asthma persisted unmodified during the intercurrent psychosis, an acute melancholia.

In the case of a young man personally observed by the writer, the asthma seemed to be mitigated during the periods of the psychosis, but never entirely. Houckgeest (*Nederlandsch. Tijdsch. v. Geneeskunde*, May 11, 1918).

ETIOLOGY AND PATHOLOGY.—Heredity shows itself in about one-half of the cases when three generations are included in the computation. If diathetic diseases such as rheumatism, gout, migraine, etc., are included as predisposing factors, as taught by Trousseau, almost every case will be found to be hereditary.

Asthma presents itself before the age of 10 years in one-fourth of the cases, but it may occur at any period. It is more frequent among males than among females. The wealthy are more prone to it than the poor, owing to dietetic errors and sedentary habits, the latter cause also explaining the disease's predilection for persons deprived of physical exercise, such as clergymen, lawyers, clerks, etc. Autointoxication of intestinal origin, often due to sedentary habits, and termed "stercoremia" has also been considered as a cause.

Atmospheric influences are active factors in the production of an attack. Excessive dryness, such as that of overheated or insufficiently ventilated rooms, or, on the contrary, excessive dampness, may bring on a paroxysm. Cases in which gout, rheumatism, etc., exist are especially sensitive to dampness.

Asthma sometimes appears during pregnancy. If the patient has previously suffered from bronchial asthma, the paroxysms of the latter may increase in intensity during gestation. The fact that the thyroid is enlarged during pregnancy is interesting, especially in view of the occasional presence of asthma in goitrous cases even though no pressure is exerted by the tumor upon the trachea.

Case of premenstrual asthma of thyroid origin. A young girl of 18, without any physical defect other than a marked hypertrophy of the thyroid gland, had generally, two or three days before her menstrual periods, attacks of asthma of sufficient intensity to necessitate medical interference. At the same time the thyroid body was vascular and tumid, and sibilant râles could be heard all over the lungs. Drugs had but little effect on the condition, which, however, passed away immediately the catamenia was established. The use of thyroid extract brought about the reduction in size of the gland to the normal. Gennari Il Morgagni (St. Louis Med. Review, Jan., 1911).

Various theories have been propounded to explain the dyspnea, but the prevailing one today is that it is due primarily to spasm of the smaller bronchi, as taught by Laennec, Biermer, and Williams, and, secondarily, by spasm of the muscles of the thorax and of the diaphragm, which are unable to cause expulsion of the air imprisoned in the alveoli on account of the restricted lumen of the bronchi.

Morbid changes also occur in the bronchial mucous membrane in some cases, attended by more or less catarrhal inflammation in which swelling—an added cause of dyspnea—is present. Some observers have attributed the paroxysms solely to this cause; but their sudden onset and, under proper medication, equally sudden disappearance, point clearly to the bronchial spasm as the predominating factor. The bronchial hyperemia is most apt to occur in asthma observed in the course of infections. I have advanced the view that the bronchial irritation which underlies the spasm was originally due to the presence in the blood of toxins, toxic wastes, etc., which are eliminated by the bron-

chial mucosa—in addition to their morbid influence on the central nervous system.

Intravenous injections of adrenalin were found to cause an increase of the respiratory excursions of the lungs. The increase, however, was less noticeable in normal animals than in those suffering from "muscarine asthma." The antagonism observed between muscarine and adrenalin made it clear, furthermore, that bronchial spasm, and not embarrassment of the pulmonary circulation, was the chief factor in the production of muscarine asthma, since it was shown that the spasm was relaxed by adrenalin. Januschke and Pollak (*Arch. f. exper. Path. u. Pharm.*, Bd. lxvi, S. 205, 1911).

The writer used **adrenalin** in 22 cases of asthma and, with 1 exception, obtained good results. In this 1 exception, there may have been a complicating emphysema. In other cases the patients were always relieved within 20 minutes. Small doses, 2 drops or even 1 drop, proved usually efficient without the by-effects produced by larger doses. Relief was always experienced within 20 minutes. Triviño (*Revista Ibero Americana*, Apr., 1918).

From my viewpoint, adrenalin and the other active principles of the adrenal secretion produce their beneficial effects in two ways: 1, by enabling the blood to take up more oxygen in the lungs and increasing, therefore, tissue oxygenation, and, 2, by enhancing the catabolism of the toxic wastes, toxins, etc., which produce the bronchial spasm.

The main difficulty of ventilation in asthma lies in the distention of the infundibula, and this fails to allow an equal diffusion of carbon dioxide throughout the alveolar air. Hoover and Taylor (*Arch. of Internal Med.*, Jan., 1915).

The writers attribute to a circulatory cause the high CO₂ content of the alveolar air in asthma and obstructed expiration in general. The rise in intrabronchial pressure during

the long expiration interferes with the free flow of blood through the pulmonary capillaries and causes a damming back of the blood on the venous side. There is a consequent accumulation of carbon dioxide in the blood with the liberation of carbon dioxide into the alveolar air. Friedman and Jackson (*Arch. of Internal Med.*, May, 1917).

The diminished lumina of the tubes and the paresis of the muscles of the chest walls may be primarily due to four classes of factors:—

1. To reflex action originating in a lesion situated in organs other than the lungs: the eyes, ears, upper respiratory tract, stomach, intestines, genitourinary system, etc. Prominent in this connection are nasal obstructions or deformities, septal spurs, hypertrophies of the turbinate mucosa, owing mainly to the pressure they exert upon the opposite side of the lesion. Onodi, in accord with my own experience, states that the nasal reflex points are especially to be found in the lower and middle turbinates, the lower portion of the septum. The maxillary and sphenoidal sinuses may also excite attacks when diseased.

In children asthma is never due to adenoids or nasal catarrh and is never influenced by operations for the latter, but it may be accompanied by a chronic catarrhal bronchitis or violent and repeated sneezing. The child outgrows the tendency and the lungs do not seem to suffer from it, but the underlying arthritic tendency persists and is liable to manifest itself in other ways. The first attack of the asthma is often puzzling; pneumonia is suspected, but the sudden onset, the normal temperature and the musical character of the râles, and their propagation and the transient character of the syndrome establish the true diagnosis. J.

Comby (Archives de méd. des enfants, Oct., 1911).

In every case search should be made for some form of chronic infection of the nasal accessory sinuses, in a chronic hyperplastic ethmoiditis, or in some closed cavity in any other part of the body, and, finding it, advise its removal by surgical interference. R. H. Babcock (Med. Rec., Aug. 2, 1913).

The writer examined the nose in 107 cases of asthma, and found the conditions such as to call for operation in 68, to be abnormal but not to call for operation in 31, uncertain but probably adenoids in 1, and no nasal abnormality in 7. Dundas Grant (Pract., June, 1913).

In about 300 cases examined at the Mayo clinic, over 90 per cent. showed the principal etiologic lesions in the upper respiratory tract, chronic supuration or retention of mucoid secretions in the nose or accessory sinuses occurring in the majority. Relief was parallel with the degree of success obtained in securing **free and continuous drainage**, little attention being paid to reflex factors. Justus Matthews (Med. Rec., Sept. 20, 1913).

The association of chronic ethmoiditis and asthma is an intimate one; a deviated septum or a similar lesion within the nose may aggravate the symptoms. Great improvement has followed the **removal of the pathological nasal lesions**. J. Mackenzie Brown (Annals of Otol., Rhinol. and Laryn., June, 1917).

The overproduction of irritating gases in the gastro-intestinal canal, which, operating physically and chemically, produce the asthmatic paroxysm. The latter ends when the irritation in the esophagus and pharynx have been removed, partly by neutralization of the irritation and partly by its dilution with pharyngo-esophageal secretions. M. I. Knapp (Med. Rec., Mar. 8, 1919).

The so-called "dyspeptic asthma" is another form due to reflex action. It may occur during the process of

digestion, the dyspnea being attended by cyanosis in some cases, or it may manifest itself only if during digestion any exertion is made. Proper treatment of any gastric disorder that may be present arrests the asthmatic paroxysms. Autointoxication of intestinal origin is another cause which is eliminated by the adjustment of the patient's diet to his needs, especially where meat nucleins, etc., are eaten in excess. (See article on Auto-intoxication and Acidosis in the present volume.) Additional data on this etiological factor are submitted below (3).

2. Irritation of the bronchial mucous membrane, in catarrhal processes, by dust of various kinds, metallic (grinders' asthma) or pollen, and the emanations of various plants, fruits, animals, etc., in beings hypersensitive to their action, or of irritating chemicals: sulphur, phosphorus, etc.

3. Irritability of the sympathetic system through the sudden arrest of peripheral disorders: eczema, urticaria, psoriasis. These cutaneous phenomena may also, however, be produced by the same agent which gives rise to the asthmatic paroxysms. Von Noorden, for instance, has called attention to the frequent occurrence of asthma among persons who, in their youth, suffered from stubborn cutaneous eruptions. Urticarial asthma due to mussel poisoning (Martyn) also exemplifies this class of cases.

4. Irritability of pneumogastric nerve following whooping-cough, measles, or infantile bronchial disorders, or through pressure upon it of enlarged bronchial glands.

The above-mentioned factors are able to give rise to the pulmonary and muscular phenomena, owing to the untoward accumulation in the system at large of (1) products of metabolism which fail to be eliminated through hematopoietic or renal insufficiency, uric acid, acetone, etc.; (2) extraneous toxics, such as lead, mercury, etc.

The influence of autogenous auto-intoxication by wastes is well illustrated by a case witnessed by Francis Taylor in which asthma replaced epileptic fits. The pent-up nerve-storm, instead of discharging itself in the customary channel in an epileptic seizure, expended its energy upon the bronchial muscular fiber, giving rise to the protracted asthmatic phenomena. After many hours it exhausted itself by way of an orthodox "fit," thus bringing the disturbance to a conclusion.

According to Huchard, the nocturnal occurrence of asthmatic attacks is to be ascribed to the greater toxicity of the urine, as compared to that of the daytime. This may be exemplified by 5 cases of arteriosclerosis reported by Pawinski in which symptoms of angina pectoris accompanied attacks of true asthma. In one of these evacuation of the bladder caused the entire disappearance of the dyspnea with surprising rapidity. The cases due to imperfect gastrointestinal digestion doubtless belong also to the class of cases in which autotoxemia is the underlying cause.

The writer has found evidence of autointoxication in every case of asthma examined by him for four years, leading him to believe that during the attack there is some toxic

in the blood which acts similarly to muscarine, or which depresses the respiratory center to such an extent that the reflex stimulation of an inflamed nasal mucosa results in a stimulation of the constrictor fibers of the vagus. Nearly every one of these cases was relieved by diminished nitrogenous diet and measures to reduce the toxemia. Eustis (*New Orleans Med. and Surg. Jour.*, Aug., 1909).

Asthmatic individuals seem to suffer from a condition of tissue sub-oxidation. Whether this is due to the lack of oxygen induced by the functional failure of the pulmonary system, or whether the suboxidation is the result of the causative factor of the disease and is, perhaps, the etiologic factor in the production of the spasmodic seizure, cannot be at the present time decided. Zugsmith and Kahn (*Arch. of Internal Med.*, Apr., 1918).

A relationship between asthma and anaphylaxis has recently been suggested. But the problem as a whole is still too obscure to warrant any conclusion.

Theory that asthma is an anaphylactic phenomenon, *i.e.*, that asthmatics are "sensitized" to a specific substance and the attack of asthma sets in whenever they are "intoxicated" by that substance. Meltzer (*Jour. Amer. Med. Assoc.*, Sept. 19, 1910).

There is a form of bronchial asthma which is undoubtedly due to a diabetic anaphylaxis toward hen's eggs. Kossler (*Ill. Med. Jour.*, Jan., 1913).

The changes in the blood with reference to the anaphylactic crisis were found by the writers to show an analogy between asthma and paroxysmal hemoglobinuria, and were able to vaccinate against the latter and to successfully remove the anaphylactic condition and secure a complete immunity. Autoserotherapy in asthma gave no positive results, however.

The authors established a change in the blood, in both diseases, *which they call "hemoclastic crisis," which consists of leucopenia, fall of arterial pressure, increased coagulability of the blood, and diminution of the refractometric index of the serum. They consider that in the asthmatic attack the respiratory symptoms, which are the only ones evident, are only one aspect of the disease, behind them being concealed an entire series of humoral changes creating in the blood-plasma physiochemical changes of which the hemoclastic crisis is the representation. The attack is, therefore, the termination of a sudden and profound disturbance which has previously taken place in the entire humoral medium. F. Widal, Lermoyez, P. Abrami, E. Bressaud, and E. Joltrain (*Presse Méd.*, July 11, 1914).

Scarification of the skin and inoculation with egg white will show whether egg albumin is the specific cause of the asthma. Many, if not all cases of egg asthma, may be immunized to egg white by feeding them with gradually increasing doses of egg albumin in capsules. Talbot (*Boston Med. and Surg. Jour.*, Nov. 5, 1914).

In the asthma in children, out of 45 cases there were 13 in which the skin test gave no clue to the etiological cause of the asthma. In one case 38 tests were made before positive information was obtained; this illustrates the difficulty of finding the cause of asthma. It was found that one individual was apt to react to more than one form of protein. A definite etiological connection may, however, be established between most cases of asthma and some foreign protein by the skin test. Experience has shown that when a positive skin test is obtained for a food and the food is then removed from the diet, the general condition of the patient almost invariably improves, and in many instances a cure results. Talbot (*Boston Med. and Surg. Jour.*, Aug. 10, 1916).

Out of 150 patients studied, 83, or 55 per cent., were sensitive to some protein and 67, or 45 per cent., were not sensitive. In the 83 sensitive cases, horse dandruff proteins were the cause of asthma in 20 per cent. of the cases; the wheat proteins, staphylococcus pyogenes aureus protein, and the early pollens were each the cause of asthma in 15 per cent.; the late pollens in 10 per cent.; cat hair protein in 5 per cent.; staphylococcus pyogenes albus protein in 3 per cent.; a group of common foods in 7 per cent., casein, egg, chicken meat, and feathers, and in the remaining 10 per cent. several proteins were the cause of asthma. I. C. Walker (*Trans. Amer. Med. Assoc.*; *N. Y. Med. Jour.*, June 9, 1917).

PROGNOSIS.—The prognosis of asthma depends upon the nature of its underlying cause. Cases of reflex asthma in which the primary disorder is easily reached and properly treated—such as nasal hypertrophies, polypi, aural growths, etc.—are frequently cured and remain so, provided the causative affection does not remain. The prognosis is also good in young subjects with well-formed chests and in whom direct heredity cannot be traced. In all others, however, the chances of recovery are very limited.

Death rarely ensues from spasmodic asthma, but its complications may prove fatal.

TREATMENT.—The treatment of asthma consists of (1) arrest of the paroxysm; (2) prevention of the paroxysms by measures calculated to annul the effects of exciting factors, and (3) removal of the pathological conditions forming the basis of the paroxysms.

1. **Paroxysm.**—Before instituting measures calculated to arrest an attack, the nature of the disorder giving rise to dyspnea as a symptom

must be carefully determined. Were a paroxysm found to be due, for instance, to a cardiac affection, the remedies most frequently prescribed—stramonium, belladonna, and the various anesthetics—would prove dangerous. When the presence of true asthma is ascertained beyond a doubt, the object should be to relieve suffering, and antispasmodics or narcotics are indicated. Two important facts must be borne in mind by the practitioner, however, namely: the danger presented by all narcotics to give rise to the drug habit, and the necessity of giving sufficiently large doses to produce physiological effects if satisfactory results are to be attained.

The **bimeconate of morphine**, $\frac{1}{4}$ grain (0.016 Gm.) by the mouth, or small doses of **morphine sulphate**, or, again, 10 minims (0.6 c.c.) of **Magen-die's solution**, given hypodermically (the dose varying, of course, with the age of the patient), are the most certain agents when rapid effects are necessary.

Fully 50 per cent. of the persons addicted to **morphine** have been victims of asthma. Yet, it is astonishing what small doses will give relief. From $\frac{1}{20}$ to $\frac{1}{12}$ grain (3 to 5 mg.) at most will generally cut the attack short and insure a night's sleep. Goldschmidt (Berl. klin. Woch., July 1, 1907).

The writer gives **heroin hydrochloride** $\frac{1}{12}$ to $\frac{1}{8}$ grain (0.005 to 0.01 Gm.) hypodermically. The dose should not exceed $\frac{1}{4}$ grain (0.015 Gm.). Fraenkel (Therap. Monats., Jan., 1912).

Morphine may be combined with **atropine** (not more than $\frac{1}{120}$ grain—0.00054 Gm.—being given in any case). **Atropine** alone has recently been urged as an excellent agent to arrest an attack.

The writer has witnessed excellent results from **atropine** in certain cases, although it is by no means a panacea in all cases. In one case he has succeeded not only in arresting the attacks with it, but the patient was improved so that there was no recurrence of the asthma for ten months, although the man had been constantly affected with it for twenty years. **Atropine** can be advantageously used as a substitute for or to alternate with **morphine**. In 7 patients with severe asthma treated with **atropine**, the results were quite encouraging. The writer prescribes the **atropine** in pills containing each 0.0005 Gm. ($\frac{1}{20}$ grain), at first 1 a day, then after two or three days gradually increasing to a total of from 4 to 6 pills a day, and then gradually reducing the dosage to 1 pill a day. P. v. Terray (Med. Klinik, Jan. 17, 1909).

Severe acute attacks of asthma are best checked by means of an injection of **morphine** with **atropine**. If seen early, the following may be prescribed: **Caffeine valerian**, 0.25 (4 grains); **theobromine sodium salicylate**, 0.5 (8 grains). One to 2 such powders to be taken at the onset. If the attack of asthma seems to be induced by bronchial catarrh the **iodine preparations** do good service. Goldschmidt (Münch. med. Woch., Nu. 43, 1910).

As held by Brügelmann, asthma is the result of irritation of the respiratory center. He has had 3510 patients with asthma during the last thirty years, and has made a special study of the traumatic, reflex, and toxic factors that may irritate the respiratory center and thus induce asthma in the predisposed. All reflexes may act on the respiratory center, reflexes from the eyes, ears, nose, throat, stomach, intestines, sexual organs, cold feet and skin, etc.

The greatest light was thrown on the whole subject, he asserts, by his observation of the effect of inhalation of an **atropine** spray. This frequently arrested at once an attack of asthma,

as also painting the nasal mucosa with **atropine-cocaine solution**. The special points where the atropine exerted this action seem to be restricted to the region behind the uvula, the tonsils and their vicinity. The asthma is at once arrested, and there is no further disturbance as long as the paralyzing action of the drug on the region lasts, no matter whether the asthma is of traumatic, reflex, or toxic origin. Weiss (*Therapie der Gegenwart*, Oct., 1910).

Codeine may be used instead of the morphine if the latter produces nausea. These remedies present, as objections, however, the partial suppression of expectoration in some cases and a certain amount of danger in cases of Bright's disease.

The adrenal active principle, **epinephrin**, or **adrenalin**, is very effective. The best effects are obtained by injecting 5 to 10 minims (0.3 to 0.6 c.c.) of the 1:1000 solution in 1 dram (4 c.c.) of the solution intramuscularly. The remedy should be used by the physician alone, however, and not entrusted to the patient who will tend to use it in excess and expose his life.

Adrenalin solution in 13 cases of acute asthma gave immediate relief, lasting for longer or shorter periods. There were no undesirable after-effects. The treatment consisted of spraying into the nose a solution of adrenalin chloride varying in strength from 1:1000 to 1:4000, according to the severity of the case. Matthews (*Brit. Med. Jour.*, Feb. 19, 1910).

Adrenalin, given by hypodermic injection in the dose of 10 minims (0.6 c.c.) of the 1:1000 solution, found in a number of cases to relax the spasm of asthma instantly. When taken by mouth it is ineffectual. In one case adrenalin injections every evening in the hay season served to ward off hay fever and accompanying asthma. Melland (*Lancet*, May 21, 1910).

Two cases of severe bronchial asthma with which the patients had been afflicted for years, and in which good results were obtained by the inhalation of **oxygen** and **adrenalin**. The writer used 15 minims (1 c.c.) of a 1 per cent. adrenalin solution. There was no increase of the blood-pressure nor any other undesirable after-effect. J. Segal (*Centralbl. f. innere Med.*, Nu. 23, 1910).

In 31 cases of bronchial asthma the writer found the most effective drug next to morphine to be **epinephrin chloride**. Hardly have the 10 to 15 (0.6 to 0.9 c.c.) drops of the 1:1000 solution been given under or into the skin, he states, when the patient will declare that he is already better. Upon investigating the question of the blood-pressure in these cases and the effect of the epinephrin upon it, the author concludes that: (1) blood-pressure is not usually high in paroxysms of asthma; (2) it is not increased by epinephrin administered hypodermically in such paroxysms, but tends rather to be lowered. In most instances the pressure was lowered about 5 mm. and returned within a few minutes to its original level.

In many cases the relief from **epinephrin**, in addition to being prompt, was lasting, the patients having a rest for longer periods than after being relieved by other means. Other patients found it necessary to demand several hypodermics in twenty-four hours. One man learned to inject the drug himself and used as many as 4 or 5 hypodermics a day, usually at night. If he took the drug in the beginning of the attack he was promptly relieved and expectorated large quantities of thick mucus. In a few cases the drug failed to relieve. I. I. Lemann (*Amer. Jour. of Med. Sci.*, Dec., 1911).

[As I have pointed out, it is by increasing the oxygen intake that the adrenal principle arrests the attack, the adrenal secretion having for its purpose, from my viewpoint, to take up oxygen in the lungs and deliver, as a catalyzer, to the tissues as

the oxidizing constituent of the hemoglobin. C. E. DE M. S.]

The dose of **adrenalin** generally used for asthmatic attacks is much greater than is necessary. The first dose tried by the writer was 3 minims (0.18 c.c.) of 1:1000 solution of adrenalin chloride. The relief of the asthma was almost instantaneous, but he felt extremely ill for some minutes, his hands shook so much that he could hardly put the syringe away, and his pulse became very rapid. Since that date he has given himself a large number of injections, but never more than 2 minims (0.12 c.c.), and rarely more than 1 minim (0.06 c.c.); for slight attacks $\frac{1}{2}$ minim (0.03 c.c.) has been sufficient. With these small doses the only effect he ever experienced is relief of the asthma, and this is invariable. Hertz (Brit. Med. Jour., May 2, 1914).

The writer reports 7 cases of bronchial asthma treated with **pituitary body** anterior lobe on the plea that the paroxysms might be due to deficient adrenal secretion. One $2\frac{1}{2}$ -grain (0.16 Gm.) tablet was given 4 times each day. Each case treated showed very marked improvement in the distressing train of symptoms in 48 hours. The duration of this treatment varied from 10 days to 7 weeks, but in no instance did it fail to make the patient comfortable in a short time. Warfel (Indianapolis Med. Jour., July, 1915).

Chloral hydrate also affords prompt relief; 15 to 20 grains (0.97 to 1.3 Gm.) may be given to an adult. Marked cardiac disorder renders this drug dangerous; the heart should be carefully examined.

Chloroform proves rapidly effective in some cases. Fifteen drops (0.9 c.c.) in a half-tumblerful of water to which a teaspoonful of syrup of orange-peel has been added make up a palatable dose. **Chloroform** anesthesia will also arrest the paroxysm, but it is not to be recommended un-

less other means have failed. A preliminary application of a 5 per cent. solution of **cocaine** to the nasal mucosa not only aids markedly to arrest the paroxysm, but reduces greatly the danger incident upon the administration of the anesthetic.

Sulphuric ether, 30 to 40 drops (1.8 c.c. to 2.4 c.c.), may also be administered by the mouth as above, or on a piece of sugar, but the sudden volatilization produced by the heat of the stomach causes eructations which are unpleasant to the patient. When used as a general anesthetic in these cases, ether tends to irritate the larynx and to enhance temporarily the distressing sensation of suffocation. Hence its use is not advisable.

Hoffmann's anodyne (compound spirit of nitrous ether), 1 dram (4 c.c.) in half a tumblerful of pure water, is frequently effective. The dose should be repeated every half-hour. **Aspirin** may prove useful when any of the agents enumerated above are not available.

The writer has obtained great relief from **acetylsalicylic acid**, as did a number of patients. The dose was 1 Gm. (15 grains). It always helped at once and served to ward off impending attacks. Some of his patients have been thus taking it for 2 years. Jepsen (Ugeskrift f. Laeger, Aug. 20, 1914).

The application to the mucous membrane of the nasal cavities of a 5 per cent. solution of **cocaine**, previously referred to when reference to the use of ether was made, is highly recommended by Dieulafoy.

The **smoke** obtained from antispasmodic remedies—**niter**, **stramonium**, **tobacco**, **hyoscyamus**, and **belladonna**—is efficacious in cases in which emphysema is not marked.

Cigarettes may be made of paper soaked in a saturated solution of **nitrate of potassium and belladonna**. The sheets are allowed to dry, and are then rolled into the shape of cigarettes.

The writer recommends the following **fuming inhalation** for many of his bronchially asthmatic patients, with remarkable therapeutic success:

R *Potassii nitratis*,
Pulv. anisi fruct. āā. ʒss (15.5 Gm.).
Pulv. stramonii fol. ʒj (31 Gm.).
 M. et ft. pulv.

A thimbleful of this powder placed upon an earthenware plate is pinched by the fingers into a pyramidal shape, and lighted at the top of the little conical heap. It burns with a smoldering and gently deflagrating flame, and is held near and beneath the patient's face, who breathes in the smoke as it issues from the burning heap of powder. The ingredients of the powder should be dry, well mixed, and finely powdered. Sawyer (*Folia Therapeutica*, April, 1907).

An effective cigarette may also be made of equal parts of **lobelia, stramonium, and green-tea leaves**, or of **stramonium leaves** and ordinary tobacco. Tobacco sometimes proves useful alone where it has not been previously used.

The local application of **epinephrin inhalant**, which is available in small, compressible tubes similar to those used for oil pigments, and the tip of which can be inserted deeply into the nostrils, is often very efficient.

The inhalation of 1:1000 **adrenalin solution** in a special very fine spray from small atomizer arrests a paroxysm at any time. In established severe attacks, the following combination is recommended: **Adrenalin solution** (1:1000) 9 c.c. (2¼ drams); **atropine sulphate**, 0.01 Gm. (¼ grain); **cocaine hydrochloride**, 0.025 Gm. (½ grain); **distilled water**, 1 c.c. (16

minims). Staubli (*Münch. med. Woch.*, Jan. 21, 1913).

On the basis of 43 cases of bronchial asthma in infants and children seen in one year at the Vanderbilt Clinic, LaFetra. Of first importance are those remedies which are administered by inhalation. In infants where attacks resemble capillary bronchitis steam impregnated with **creosote** is satisfactory in relieving the spasms. In older children the **nitrate vapors** with or without **stramonium** are efficient. **Atropine** in doses of ½₂₀₀ grain (0.0003 Gm.) every two hours until the face flushes frequently produces a prompt cessation of the spasms. After the attack has passed off, the atropine is given twice or three times a day for several days. If the attack is accompanied by gastric indigestion the stomach should be emptied at once, preferably by a dose of syrup of ipecac. For long-standing cases and those in older children the following may be given:—

R *Potassii iodidi* gr. xx (1.29 Gm.).
Morphine sulphatis, gr. ⅓ (0.021 Gm.).
Tinct. belladonna . mxx (1.23 c.c.).
Spts. ætheris comp. f3iij (12 c.c.).
Aquæ q. s. ad f3ij (62 c.c.).

On the theory that there is a vasomotor paresis the writer has given **adrenal gland** and nasal instillations of **adrenalin chloride** solution with marked benefit.

The famous **hyoscyamus** and **stramonium cigarettes of Espic** are composed of the following agents:—

R *Belladonna leaves* .. 6 grs. (0.39 Gm.).
Hyoscyamus leaves,
Stramonium leaves,
 of each 3 grs. (0.19 Gm.).
Extract of opium .. ¼ gr. (0.016 Gm.).
Cherry-laurel water . q. s.—M.

The most active principle in the above combination being **pyridine**, the cigarette may be replaced by inhalations of the drug, 10 to 15 drops (0.6 to 0.9 c.c.) being inhaled from a handkerchief. The following method of using pyridine, however, is the most effective:—

The patient being in a small room, a saucer containing pyridine is put

some distance from him. He is allowed to inhale the fumes about half an hour (Germain Sée, Chicot, Kelamin, Dieulafoy).

Pyridine is the drug *par excellence*; its physiological effect is to diminish the reflex activity of the medulla and respiratory center; 10 to 15 drops (0.6 to 0.9 c.c.) inhaled from a handkerchief give almost instantaneous relief. **Iodide of ethyl** is used in France, and much praised. It is put up in glass capsules containing 6 drops. W. A. Wells (N. Y. Med. Jour., Oct. 13 and 20, 1900).

Hyoscyamine, $\frac{1}{140}$ to $\frac{1}{120}$ grain (0.00048 to 0.00055 Gm.) given hypodermically, is recommended by S. Solis-Cohen, Musser, and others.

Paraldehyde, 30 minims (1.94 c.c.) hourly until improvement is noted, is recommended by Mackie and others.

Passion flower (*passiflora incarnata*) possesses hypnotic and antispasmodic powers, and in sufficient dosage it would probably act as a narcotic poison. Even in moderate doses it may in some cases provoke nausea and emesis. The combination of relaxant influences gives it peculiar value in allaying asthmatic paroxysms and in preventing their full development. It may be given in tincture or fluidextract. The dose is from 10 to 30 minims (0.6 to 1.8 c.c.) well diluted and given from every ten minutes to every half-hour until relief is experienced, emesis caused, or drowsiness induced. Half a fluidounce (15 c.c.) of the fluidextract has personally never been exceeded in the course of two hours. Patients have fallen asleep after 6 doses of 10 to 20 drops (0.6 to 1.2 c.c.) each, given every ten or fifteen minutes, or after a single dose of 1 fluidram. In 2 out of 8 cases its use produced but slight mitigation of distress, and was abandoned. In 6 cases rebellious to other methods it gave prompt relief. S. Solis-Cohen (Amer. Medicine, Sept. 14, 1901).

Of the remedies employed to ward off an attack, **caffeine iodide** the most useful. For patients who cannot take even the smallest amounts of iodide without symptoms of iodism, the writer gives 5 to 10 grains (0.32 to 0.64 Gm.) of **calcium chloride** before or after the caffeine iodide. They cannot be dispensed together, as calcium iodide is formed and the calcium no longer controls iodism.

Other combinations of value are:—

I.

R Nitroglycerin gr. $\frac{1}{200}$ to gr. $\frac{1}{100}$
(0.0003 to 0.0006 Gm.).
Sodium iodide .. gr. iij to gr. v
(0.2 to 0.3 Gm.).

One dose to be repeated every two or three hours until the attack subsides.

II.

R Sodium nitrite gr. ss to gr. j
(0.032 to 0.065 Gm.).
Sodium iodide .. gr. iij to gr. v
(0.2 to 0.3 Gm.).

Give every two or three hours.

III.

R Fluidextract of grindelia robusta . m̄xv to m̄xxx
(0.9 to 1.8 c.c.).
Sodium iodide .. gr. ij (0.13 Gm.).
Nitroglycerin gr. $\frac{1}{200}$ (0.0003 Gm.).
Tincture of euphorbia pilulifera. m̄xx (1.2 c.c.).
Spt. of chloroform
q. s. ad. 3j (4 c.c.).

M. Sig.: One to 2 teaspoonfuls in water every two to four hours while the attack lasts.

IV.

R Fluidextract of grindelia robusta,
Fluidextract of myrtus chekan,
Fluidextract of yerba santa,
of each m̄xx (1.2 c.c.).
Fluidextract of quebracho 3j (4 c.c.).

M. Sig.: One dose to be taken in 2 teaspoonfuls of brandy in half a tumblerful of water.

Morphine may be given hypodermically in conjunction with hyoscine, as in the following:—

℞ *Morphine hydrochloride* . gr. $\frac{1}{6}$ (0.01 Gm.).
Hyoscine hydrobromide . gr. $\frac{1}{2000}$ to gr. $\frac{1}{4000}$ (0.0003 to 0.0006 Gm.).

To the foregoing, $\frac{1}{200}$ grain of **nitroglycerin** may be added, or **atropine sulphate** may be substituted for the hyoscine.

As a useful form of vaporized spray solution the writer recommends the following:—

℞ *Cocaine hydrochloride*,
Atropine sulphate,
of each gr. ij (0.13 Gm.).
Sodium nitrite .. gr. x (0.65 Gm.).
Glycerin ℥xx (1.2 c.c.).
Rose water, q. s.
ad ℥ss (15 c.c.).

M. et sig.: Five or 10 minims to be inhaled through the nose by means of a very fine vaporizing spray. Repeat at intervals of twenty to thirty minutes if necessary. P. W. Williams (Practitioner, Oct., 1910).

Calcium salts being sedatives of the nervous system, it was tried with success in 13 cases of asthma and allied conditions. It was given in the form of 20 Gm. (5 drams) **calcium chloride**; 40 Gm. (10 drams) simple syrup, and distilled water, to 400 Gm. (13 ounces). The patient took a tablespoonful of this in milk every two hours for eight days. No untoward by-effects were observed in any instance, and the patients all said that after a day or so they could breathe and expectorate easier and their sleep was no longer disturbed. After the third day there were no further attacks in all but 2 cases. Kayser (Therap. Monats., March, 1912).

Constantly successful results in asthma from combined administration of **strontium bromide** in large doses and injections of **camphorated oil** 2 c.c. (32 minims). As a preliminary measure, salt should be at least in part proscribed from the diet. In adults the daily dose of the bromide

is 4 Gm. (1 dram); occasionally as much as 6 Gm. ($1\frac{1}{2}$ drams) is required. On the first day, 2 injections of a 10 per cent. solution of camphor in oil, 2 c.c. (32 minims) at a dose, are given. Improvement occurs promptly, at times immediately. Camescasse (Presse méd., Dec. 20, 1917).

Antipyrin, 15 grains (1 Gm.) being given every three hours until the access is relieved, proves especially effective in anemic cases; but such large doses are toxic in some cases. Again, it sometimes does harm in increasing the severity of subsequent attacks, particularly in a case associated with bronchitis.

Caffeine citrate—1 to 5 grains (0.065 to 0.32 Gm.), dissolved in warm water every four hours—is especially effective in bronchial asthma and in bronchitis associated with spasm of the bronchial tubes. **Theobromine** has also given good results.

Theobromine sodiosalicylate, possessing a vasodilator action, is very useful in bronchial asthma, both in the so-called nervous type and in the catarrhal form of the affection. At the inception of the attack the writer prescribes 15 grains (0.9 Gm.) dissolved in water; if relief is not apparent in fifteen minutes a second dose is given; rarely is a third necessary. In most instances the condition is much ameliorated and sometimes the attack is terminated entirely. No tolerance to the drug is established, and it may be taken daily for a considerable period. Renal and circulatory lesions may contraindicate its administration. Von den Velden (Münch. med. Woch., Bd. xiv, S. 697, 1907).

Glonoin, composed of 1 part of nitroglycerin to 99 parts of alcohol, given in doses of $\frac{1}{100}$ to $\frac{1}{50}$ grain (0.00065 to 0.0013 Gm.), acts rapidly in some cases; but even in these its

effects are frequently only temporary. From 2 to 5 drops (0.12 to 0.3 c.c.) of a 1:100 solution of **nitroglycerin** (if there is but little emphysema and no cardiac disorder) are recommended by Woodbury and Hoffmann.

Laborde's **rhythmic traction of the tongue** might be tried when no remedies are within reach. The organ being held by the fingers, covered by a napkin, it is drawn out at regular intervals, eighteen to twenty times a minute, imitating the respiratory rhythm.

2. Prevention of Paroxysm.—As already stated, the phenomena observed in the chest walls and lungs may be due to reflex action, the primary factors of which may be located in the nasopharyngeal tract, the ear, the digestive tract, and the genital organs.

Careful examination of all the organs becomes, therefore, imperative. The nose and stomach are, doubtless, most frequently at fault. In the nasal cavities the lesions met with in the majority of cases are nasal polypus, deflected septum, and turbinal hypertrophy. The sinuses including the antrum may also, when diseased, cause asthma reflexly. Active measures to remove any of these abnormalities should be instituted whenever found, although they may not apparently interfere with the physiological functions of the nose.

That permanent relief is to be expected in one-half of the cases cannot be affirmed. An average of about 20 per cent., however, probably represents the cures obtained by rhinologists at large by the surgical measures in the nasal cavities.

Disorders of digestion, by serving as preliminary factors of imperfect

metabolism, very frequently act as starting points of paroxysms in asthmatic individuals. Indeed, the majority of patients soon learn that certain articles of food and any indiscretion as to quantity or as to the time of the day at which aliments are partaken of may give rise to an exacerbation of their trouble. Experience teaches them that the greatest discretion should be observed; that easily digested food should alone be taken, especially toward evening, and that wines and alcoholic beverages had best be avoided, owing to their inhibitory influence over the various digestive processes. Gaseous liquids are also pernicious by causing dilatation of the stomach and pressure upon the overlying diaphragm. Butchers' meat, greasy soups, coffee, sweets, and other substances tending to the formation of urea are contraindicated. Milk, fish, eggs, and vegetables (except beans and rye) should form the bulk of the patient's diet.

Under this head belong also the agents which enhance catabolism of the toxic wastes, to which the attacks are due in a large proportion of subjects. Diphtheria **antitoxin** probably procures its benefit by a process of this kind, increasing directly the antibodies in the blood-stream, but its use is attended with considerable danger, having caused several deaths. Its use is, therefore, not advocated in view of the fact that many safe remedies of equal value are available.

Having published a letter asking for reports of cases in which the injection of **diphtheria antitoxin** had been followed by alarming symptoms of death, especially noting whether there was any history of asthma in the cases, out of 23 cases in which

the information was definite and positive, 16 gave a history of some form of respiratory disease. Six of the 16 patients died and 10 went into a state of collapse, with final recovery. Seven of the 23 gave no history of a respiratory distress. Four of the 7 cases died, and 3 went into a state of collapse, with final recovery. There is a danger if any form of horse serum is used in subjects who have suffered from any form of respiratory embarrassment such as asthma, the so-called cardiac or renal asthma; hay fever, with resulting asthma, subjects liable to irritation of the mucous membranes when about a horse or stable. Collapse or death was accompanied by a respiratory crisis, and, when death occurred, it took place usually in less than ten minutes from the time of injection. H. F. Gillette (Jour. Amer. Med. Assoc., Feb. 13, 1909).

Although convinced that antitoxin gives some positive relief in asthma, there is a large psychical element involved. The writer has therefore ceased to use **antitoxin**. Parker (N. Y. State Jour. of Med., Jan., 1911).

Pituitary gland, recommended by S. Solis-Cohen, and **corpus luteum** probably produce their effects by stimulating the structures which produce antibodies. **Thyroid gland** is now known to favor the production of opsonins. These, by sensitizing the toxic wastes, render them more vulnerable to the action of the antibodies, thus reaching the same results indirectly. I find 1 grain (0.065 Gm.) of the desiccated thyroid three times daily necessary to obtain satisfactory results. Large doses, by promoting excessive tissue waste, do more harm than good.

Preparations of the **pituitary gland**, and more especially of the infundibulum or posterior lobe, recommended. There are at least two, and pos-

sibly several, good commercial preparations now available. From the recoveries personally observed to follow their use in Quincke's edema, asthma, recurrent erythema, and other angioneuroses, as well as their effects in "opening" the nasal passages, they are probably superior to the adrenal preparations in all varieties of hay fever. The action is slower, but more persistent. The pituitary extracts may be used both topically and systematically. While more effective by hypodermic injection, they also produce clinical results when administered by the mouth, —another advantage over the adrenal extracts. S. Solis-Cohen (Med. Rec., May 28, 1910).

Good results were obtained in 23 cases of asthma from the use of **thyroid gland**. Many of these were cases of a number of years' standing, and had frequent, intense paroxysms, upon which thyroid preparations exerted an immediate, continued, and very marked inhibitory effect. Léopold-Lévi (Arch. gén. de méd., Mar., 1912).

Combined injections of 0.0008 Gm. ($\frac{1}{80}$ grain of **adrenalin** and 0.04 Gm. ($\frac{1}{2}$ grain) of **pituitary extract** in 1 c.c. (16 minims) of water used with marked success in arresting paroxysms in 300 cases. It was more effectual than **adrenalin** alone. A second injection was required in only 10 instances. Weiss (Deut. med. Woch., Sept. 19, 1912).

3. Curative Measures. — The removal of whatever organic disorder that may be present, whether located in the nasal cavities, stomach, genital tract, etc., is, of course, the primary feature of the treatment of a case when the existence of any such disorder can be distinctly established. The chances of cure are greatly increased when a localized affection is present, even if only concomitantly, as successful treatment of the latter entails the removal of a disturbing

element of which the sympathetic system at large and the vasomotors in particular bear the brunt. Diathetic affections,—syphilis, for instance,—and any of the conditions mentioned of which uricacidemia is the most prominent type, also require active interference. Considerable improvement, and in some cases cure, may be expected if a proper diagnosis of the primary etiological factor is established and the proper measures instituted.

Underlying the varieties of primary disorders, to which mention has just been made, are others that may be classed as complications. These are usually present whatever may be the primary cause of the disease. Most prominent among these are: 1. The general neurosis forming the basis of the asthmatic paroxysms, which may have assumed a chronic type through depravity of the nerve-centers. 2. Inflammatory lesions of the bronchial tract, which, through the supplementary congestion induced by an unusual atmospheric condition or a dietetic error, may suddenly cause a paroxysm. 3. Malformation of the thorax,—the “barrel-chest,” due to excessive distention, which may prevent the expulsion of a sufficient amount of tidal air and interfere with oxygenation,—a condition present in the great majority of cases and a potent element in the causation of suffering.

When, therefore, judicious treatment of any abnormal condition of the upper respiratory, digestive, or genitourinary tract or the circulatory and hepatic systems does not yield satisfactory results, it is probably due to the fact that either one, two, or all three of the conditions outlined

complicate the case. In the vast majority of cases of long standing the entire symptom-complex is present: a pernicious cycle that only persistent effort on the part of the physician can command. An important feature is to insure free action of the intestines. **Olive oil**, 4 ounces (120 Gm.) injected into the rectum on retiring, and kept therein until morning, insures an evacuation.

Bronchial asthma is frequently dependent upon enterogenous auto-intoxication. The writer obtained permanent cure in such cases by combating chronic coprostasis, and recommends particular attention to regulation of this eliminatory function in all cases of asthma. Ebstein (*Deut. med. Woch.*, Oct. 19, 1911).

The writer's experience has confirmed the curative value of **parenteral protein therapy** and of **benzyl benzoate** and **calcium chloride**. His formula is: 20 Gm. (5 drams) benzyl benzoate; 16 Gm. (4 drams) gum acacia; enough of a 50 per cent. solution of calcium chloride to make 200 Gm. (6¾ ounces). Five times a day 10 c.c. (2½ drams) are inhaled, using an ordinary inhaler. **Psychotherapy** is a valuable adjuvant, also refraining from meat, fish, beans and peas. He has had patients lose their asthma completely on a **purin-free diet**, without other measures. Other patients have been cured by injections of small amounts of the **protein** presumably responsible. Van Leeuwen (*Nederlandsch Tijdschrift v. Geneeskunde*, Feb. 5, 1921).

Asthenia may be said to be present in all cases of asthma. This is met most satisfactorily by **strychnine** in increasing doses, beginning for adults with 1/60 grain (0.0011 Gm.) after each meal and gradually bringing the dose up to 1/20 grain (0.0032 Gm.) during a period covering two months.

The case should, of course, be care-

fully watched, and, if the physiological effects of the drug appear, the dose of strychnine should be reduced. **Static electricity**, by stimulating the peripheral vasomotors, greatly enhances the action of the strychnine, and, in fact, is a necessary accompaniment. Daily sittings of fifteen minutes each are required to sustain the beneficial effects obtained. The **high-frequency current** has also been used with success.

When bronchial lesions are present,—they are invariably discernible in true asthma,—the treatment should begin by a course of **iodide of potassium**, rapidly increasing the dose from 5 to 30 grains (0.32 to 1.94 Gm.) three times a day. To avoid, as much as possible, gastric disturbances, it should be administered in not less than a half-tumblerful of pure water at first, and in a tumblerful when larger doses are to be taken. **Fowler's solution**, 3 minims (0.18 c.c.) three times a day, generally counteracts the eruption and other unpleasant effects of iodide of potassium, and should be administered simultaneously if need be. After a couple of months the strychnine and static electricity course may be begun. Iodide of potassium is contraindicated in cases in which there is a tendency to hemoptysis, or when there is an in-fraglottic disorder.

Treatment in the intervals between paroxysms should be addressed to the etiological factors acting reflexly—deflected nasal septa, sensitive points near the inferior turbinates, disordered stomachs, and constipation—and a reduction cure where obesity is present. The sheet-anchor in the drug treatment of asthma is iodine. A prolonged course of 10 to 15 grains (0.65 to 1 Gm.) of **potassium iodide**,

three times daily, should first be given, and thereafter ten-day periods of the use of the drug alternated with ten-day periods of intermission. I. I. Lemann (*Amer. Jour. Med. Sci.*, Dec., 1911).

Hydrotherapy in the form of cervical or spinal cold douches has also been advocated. The **sudden application** of a jet of **cold water** to the back of the neck often controls an attack of asthma.

The barrel-chest, when due to the disease, is only met with in advanced cases. But, whether present or not, the conditions acting as its causes are generally present, namely: weakness of the muscles concerned in the performance of the respiratory act, including the diaphragm. The treatment of all cases of asthma should, therefore, include measures designed to increase nutrition of these muscles and the activity of their nervous supply. **Strychnine** fulfills the latter objects, but it must be assisted by complementary measures designed to localize, as it were, its beneficial influence.

For the superficial muscles of the chest, **massage**, first along the intercostal spaces, then over the large muscles, the deltoids especially; the outline of the muscles should be borne in mind and the active pressure exerted along the muscular fibers toward the arterial trunk supplying each set. For the diaphragm the **faradic current** alone is of service, the negative pole being applied over the course of the phrenic nerve just above the clavicle and the positive over the xiphoid cartilage. The sponges being fully moistened with salt water and applied, the patient is directed to empty his lungs of air, then to *only*

inflate them partially, and to continue this restricted respiratory act during the entire sitting,—about five minutes at first, then ten minutes. The oftener this procedure will be undertaken, the sooner will satisfactory results be attained.

At home the patient will enhance the effects produced by a daily **calisthenic exercise**, consisting in bringing the fists up to the shoulders and approximating the elbows anteriorly as much as possible with each expiration. Chairs have been invented by means of which the exaggerated expansion of the thorax may be counteracted.

There are asthmogenic points in the bronchi as well as in the upper respiratory tract. By attacking these points directly by topical endobronchial applications of **cocaine**, **epinephrin solution**, etc., there has been laid the foundation for a new means of combating and conquering bronchial asthma. The writer has treated in this manner 53 patients; of these, 21 were cured by a single endobronchial application, and 14 after repeated treatment. The other patients were more or less improved, while in 7 there was no improvement. W. Freudenthal (N. Y. Med. Jour., June 24, 1911).

In many cases of asthma occurring during the menopause, natural or artificial, the administration of **ovarian substance (corpus luteum)** relieves the dyspnea along with the other symptoms of the menopause. Fishberg (Med. and Surg., Jan., 1918).

The patient should also be taught to obtain control over his respiratory muscles. As stated by Talma, the spasm of the respiratory passages may be produced voluntarily by the majority of asthmatic patients and by many normal individuals. Almost all asthmatics can control the spasms

even during an attack, but certainly during the period of remission. The muscles of the respiratory passages are either under the control of the will or may be brought under such control. As a consequence of these conclusions the importance of **respiratory gymnastics** for asthmatic patients is patent. The number of respirations per minute must be reduced and expirations performed slower and more completely. The spasm of the muscles will thus be controlled. The speech must be regulated, and while speaking the patient must inspire slowly and deeply. The asthmatic must learn to maintain the proper tension of the muscles of the neck, chest, and abdomen.

Compressed air, the patient being placed in pneumatic air-chamber in which the air has been condensed, is of great value in bronchial asthma and secondary emphysema. Unfortunately, the apparatus required is so bulky and expensive that it is hardly ever at the disposal of the physician. Expiration into rarefied air is of signal value in spasmodic asthma, the apparatuses of Waldenburg and Solomon Solis-Cohen being especially efficient for the purpose. I employ the **Guillemin hydraulic apparatus**, owing to the fact that no weights are required and because its diminutive size causes it to occupy but little room as compared with other instruments.

Strophanthus, 10 grains (0.65 Gm.) three times a day, has been credited with curative properties, but the best that can be said of this drug is that it seems to lengthen the interparoxysmal periods.

Intralaryngeal injections for the purpose of reducing the catarrhal

process of the bronchial mucous membrane have been followed by satisfactory results.

The quantity of the solution injected and the amount of the agents contained in each injection must, of course, be in accordance with the patient's age and condition. Bowie, referring to the solutions described below, states that 1 dram (4 Gm.) will be sufficient for a child from 5 to 10 years of age, 2 drams (8 Gm.) from 10 to 15; after this, from 3 to 5 drams (12 to 20 Gm.) will suffice at each sitting.

First solution: a 5, 10, 15, or 20 per cent. solution of **menthol in almond oil**.

Second solution: 2 to 5 minims (0.12 to 0.3 c.c.) of a 2½ per cent. solution of pure **crystals of iodine in almond oil** added to each dram of the first solution.

Third solution: 5 minims (0.3 c.c.) of a 10 per cent. solution of **oil of hops in almond oil** added to each dram of the first.

Ephraim's endobronchial method of treatment. Intratracheal sprays are insufficient to reach the bronchioles; the spraying must be done in the bronchi themselves. The instruments consist of a rubber tube with equidistant markings and a special conical and slightly bent spraying tip. The other end of the tube is connected with a 15-c.c. (½ ounce) receptacle in which are placed the solutions to be introduced. Joined to this system is a tube from a compressed oxygen tank, with a safety valve blowing off at 1 kilogram pressure. The larynx is first anesthetized with **alypin-epinephrin solution**, next the upper trachea, and the larynx again with **alypin-epinephrin** or **cocaine spray**, and then the lower trachea and roots of bronchi with a 1 per cent. spray of **quinine and urea**

hydrochloride and epinephrin solution. Sourdille (N. Y. Med. Jour., from Presse Méd., Feb. 14, 1914).

In Killian's clinic the results from the use of **novocaine-epinephrin solution** sprayed into a bronchus through the bronchoscope have not been as encouraging as those published by others. One patient had no further attacks for 9 months, but they returned; 6 others escaped attacks for periods of 2 to 12 weeks. One patient did not improve at all. Stephan (Deut. med. Woch., Jan. 27, 1916).

Intratracheal treatment of asthma was tried by the writer in 15 cases and 7 may be regarded as cured, no attacks having returned during about a year to date. Six were much improved but still have an occasional attack and return for further treatment. The attacks are rare, however, and much milder. De Levie (Nederlandsch. Tijdsch. v. Geneeskunde, Jan. 26, 1918).

X-rays and electric light baths have also had advocates, but these measures have been insufficiently tried to warrant more than a mention of the fact.

Vaccines, particularly the autogenous have proven effective in properly selected cases.

The **vaccine treatment** is not recommended to the exclusion of other measures, although results have been good, but simply as an aid where these fail to afford relief. He advises the patient, even when supposed to be cured, to have occasionally a few protective inoculations against any organisms to which he is sensitive, and more especially before the onset of winter. Pirie (Brit. Med. Jour., June 14, 1913).

The writer found that **autogenous vaccines** benefited asthma only when an anaërobic fusiform bacillus has been largely present in the vaccine. Great care should be exercised in the use of vaccines that the dosage be not so large or so often given as to cause reaction, since this reaction,

whether general or local, indicates a negative phase and aggravates the patient's condition. New vaccines should be prepared whenever the condition of the patient seems to have come to a standstill. R. H. Babcock (*Lancet-Clinic*, Feb. 12, 1916).

The writer following the methods of his associate, E. C. Rosenow, was able to isolate from the sputum of a number of cases of bronchial asthma streptococci which, when inoculated into susceptible animals, produced characteristic changes in the lungs. The characteristic localization of the organisms in the lungs was in the muscular coat of the bronchi. These findings harmonize with the recent observations regarding the specific affinities of many strains of streptococci with many of the clinical features of spasmodic asthma. S. Oftedal (*Jour. Amer. Med. Assoc.*, May 27, 1916).

About 1 in 6 of the non-sensitive patients treated by the writer was relieved of asthma for several months by vaccines made from a diphtheroid organism, which was a predominant organism in their sputum. The serum of about 1 in 8 of the non-sensitive patients agglutinated *Staphylococcus pyogenes aureus* and vaccines of this organism relieved the patient of asthma for several months. Patients who were sensitive to food proteins were relieved of asthma by the omission of these foods from their diet. Those sensitive to bacterial proteins were relieved of asthma by vaccines of those organisms to which they were sensitive. Patients who were sensitive to the proteins in horse dandruff and in cat hair were relieved by subcutaneous injections of these proteins; these hair proteins did not desensitize against serum, nor did serum injections desensitize against the hair proteins. When chronic bronchitis was associated with asthma, vaccines were often necessary in conjunction with the protein injections. Walker (*N. Y. Med. Jour.*, June 9, 1917).

Autogenous defibrinated blood, obtained preferably during the attacks of asthma, serves as antigen for treatment by active immunization. The writers report 6 cases thus treated which showed improvement through a diminution in the severity and frequency of the attacks, a gain in weight, an increased ability to work, and improved subjective symptoms. Kahn and Emsheimer (*Med. Rev. of Rev.*, May, 1917).

The writer treated 16 cases with an **autogenous vaccine** obtained from bacteria cultivated from the sputum. The bacteria were primarily *Streptococcus viridans* or *Streptococcus hæmolyticus* and secondarily *Micrococcus catarrhalis*. The vaccine is best given twice a week in constantly increasing strength for twelve to twenty injections, and it is better to give such doses that local reaction occurs. His initial dose is 100 millions in adults; then he proceeds cautiously until a local reaction sets in. Of the sixteen patients twelve were cured, three improved, and one tuberculous patient was unimproved. M. H. Sicard (*Amer. Jour. Med. Sci.*, June, 1917).

Out of 37 cases of bronchial asthma, 27 had distinct nasal factors which were corrected, and in addition **autogenous vaccines** were administered. Seven had 2 series of injections consisting of 15 doses. Five have been free from symptoms for over 4 years, and 9 had a return of their symptoms, but have stated that their attacks were not as severe or so frequent as before treatment. Ten patients were not benefited. M. J. Gottlieb (*N. Y. Med. Jour.*, Aug. 18, 1917).

Weil found that the injection of peptone exhausts the anaphylactic mechanism and leads to desensitization irrespective of the nature of the sensitizing antigen. Since the desensitization is quite non-specific, skin tests for the causative specific antigen are not required. This can be accomplished by a single large dose, but the effects are relatively short

lived and better results are secured by small and increasing doses extending over a considerable period of time. In some cases the large initial dose may be required, followed by smaller and decreasing doses, but it is not the plan to be recommended. The dose of peptone stops the attacks for periods roughly proportional to their previous frequency; thus if the attacks occurred weekly the remission should last from 6 weeks to 2 months, while freedom for 3 or 4 months should follow if the attacks occurred at intervals of 3 weeks. The only peptones to be used are Witte's or Armour's "ordinary" peptone, since these are the ones which contain sufficient of the primary proteoses. A 2 per cent. solution of Witte's or a 5 per cent. solution of Armour's are the most convenient for use. The peptone should be dissolved as far as possible in three quarters of the desired volume of normal saline by agitation and warming to 37° C. Then 1 c.c. (16 minims) of a 2 per cent. solution of **sodium carbonate** should be added for each 0.33 Gm. (5½ grains) of peptone to secure the requisite fineness of the suspension. The whole is then brought up to the desired volume with normal saline, adding **phenol** to 0.25 per cent. The initial dose should be about 0.3 c.c. (5 minims), which should be increased by about 0.2 c.c. (3 minims), every fifth day until 6 doses have been given, when the dose then reached should be continued for 3 or 4 more injections. Injections should not be given during attacks. A. G. Auld (Brit. Med. Jour., July 20, 1918).

Idiosyncrasies, diatheses, and predispositions of all sorts are conceived of by the writer as being due to antigens and a state of anaphylactic hypersensitiveness, inherited or individual, lasting or evanescent. Undoubtedly in most cases the alimentary tract is the focus of formation of the antigens; hence it is in the intestinal flora that the antigens required for **antianaphylactic treatment** of

gastrointestinal, pulmonary, or cutaneous disorders should be sought. In a man of 47 who had suffered 5 years from asthma every night, marked improvement followed 2 series of 10 injections of a bacterial preparation isolated from the intestinal flora and sterilized by heat. The improvement began with the first injection. A case of perianal eczema and 3 out of 4 cases of psoriasis were similarly cured, the exception being a case in which the preparation was ingested instead of injected. In all these cases virtually three-fourths of the total benefit accrued within 24 hours after the first injection. The treatment is conceived of as removing the excess of antibodies which is the immediate cause of the attacks of dyspnea or skin lesions. Similar results were obtained in numerous cases of dyspepsia with epigastric pain and of painful enteritis or enterocolitis with constipation or diarrhea. It is not necessary to employ precisely the specific material for injection. In most cases it was found sufficient to grow on ordinary agar, in separate colonies, all the aerobic organisms that would develop under these conditions, mix them in their approximate proportions in the feces, sterilize the emulsion by heat, and administer it by injection or ingestion. J. Danysz (Presse méd., July 18, 1918).

When the asthma occurs in connection with pregnancy **viburnum prunifolium** is a valuable remedy. If there should be any indication of abortion, **chloral hydrate** may be administered simultaneously.

In a paper based on 140 cases, the writers urge anew that one factor which helps and perhaps augments an asthmatic attack is the lessened alkalinity of the blood and tissues, and that the administration of large doses of **sodium bicarbonate** or **sodium citrate**, until the reaction of the urine is blue to litmus, seems to be an essential part in the treatment.

While the urine was kept alkaline, nearly all their cases were treated with subcutaneous or intramuscular injections of **soamin** (a sodium arsanilate) used at first in 1-grain (0.065 Gm.) doses, then after 4 days $1\frac{1}{2}$ grains (0.1 Gm.), and so on until the dose was increased to 5 grains (0.3 Gm.). Three or 4 weekly injections of 5-grain (0.3 Gm.) doses completed the course. Nearly 96 per cent. of cases so treated were relieved, and fully 75 to 80 per cent. were cured and are remaining free from attacks. The longest period of immunity from attacks was 3 years in a patient who used to have a paroxysm every second or third day before treatment was begun. An important feature is that throughout the treatment the urine be kept alkaline. Soamin should not exclude palliative treatment. Any disorder that may serve as the starting point of an attack, including lues or tuberculosis, should be adequately treated. Roy and Bose (Calcutta Med. Jour., June, 1918).

Climate is thought to bear considerable influence upon the explosion of asthmatic paroxysms. The fact is that very few cases are permanently cured by a change of residence, and that practically all are momentarily benefited by any change they may make. Thus, removal from the purest mountain air to the dusty air of a large city is fraught with momentary relief. It is probable that the change of diet and habits has much to do with the result attained, unless the paroxysms are greatly under the influence of bronchial catarrh, when the removal from a cold and damp climate to a warm and dry one may prove of lasting benefit. In seeking for a climate it is well to remember that, as stated by Brügelmann, for a time immunity from attacks may be apparent, but finally acclimatization

takes place and the symptoms reappear. F. I. Knight reported the case of a physician who changed his residence and practice several times during his life, on account of asthma, and who finally got relief by going back to the place from which he started. Tucson, Arizona, and Colorado in the United States, Mont-dorelles-Bains in France, the Engadine in Switzerland, and Bournemouth in England are well spoken of in this connection.

CHARLES E. DE M. SAJOUS,
Philadelphia.

ASTIGMATISM.—This term, proposed by Dr. Whewell, has been adopted, with slight modification, in all modern languages. The shorter form *astigmia* is coming more into general use.

DEFINITION.—That error of refraction by reason of which rays, coming from a single point and passing through the refractive surfaces of the eye, are not turned toward a single point, and, therefore, cannot be perfectly focused on the retina. The word astigmatism is often used alone to denote regular astigmatism.

IRREGULAR ASTIGMATISM.

DEFINITION.—The form of astigmatism arising from irregularity of a refractive surface or of the refractive index of the cornea or lens, so that rays passing through different parts of these surfaces are turned in various directions and can never be brought to a perfect focus.

Out of 1000 eyes examined by the writer the absolute astigmatism and the corneal astigmatism were the same in 475 cases—that is, 47.5 per cent.; 230 were hypermetropic, 353 showed compound hypermetropic as-

tigmatism, 89 were myopic, 190 showed compound myopic astigmatism, and 138 mixed astigmatism. J. Rowan (Brit. Med. Jour., Jan. 13, 1912).

SYMPTOMS.—There is imperfect vision, the blurring being proportioned to the degree of the defect and the size of the pupil, and affecting the seeing at all distances and all times. An eye subject to this defect is permanently "weak," cannot attempt work requiring very accurate seeing, and is liable to be strained in reading, sewing, etc. The irregularity of surface is generally accompanied by more or less haziness or opacity. This may be the opacity remaining in the cornea when irregular astigmatism has been caused by corneal inflammation, or it may be an opacity of the lens, when such astigmatism is the forerunner of cataract.

Pronounced irregular astigmatism causes *monocular diplopia*, or *polyopia*. A lamp-flame or the moon at night is seen multiplied, the different images of it usually overlapping each other more or less. It also shows itself by the distortion of letters, and in the appearance of additional lines about or upon them, plain type being made to appear like fancy type. The "rays" which appear to proceed from a point of bright light, as a star or a distant electric lamp, are due to irregular astigmatism. An eye free from astigmatism would see a star as a mere point of light.

ETIOLOGY.—Some irregular astigmatism is present in all normal eyes. When it causes no impairment of vision, below the usual standard of 20-xx, it is called normal. Normal irregular astigmatism is generally caused by the inequality of curvature in the periphery of the dilated pupil, this being cut off when the pupil contracts.

Irregular astigmatism may be due to changes in the lens preceding cataract or to irregularity of the surface of the cornea, as from abrasion or superficial ulceration.

General bulging of the cornea is commonly not uniform and gives rise to irregular astigmatism, the common form being conical cornea; but the most common cause is incomplete restoration of the corneal tissue to normal after keratitis. Peripheral groove formation and consequent bulging of the cornea cause irregular astigmatism of high degree.

Does pterygium cause astigmatism?

The prevailing theory seems to be that a pterygium begins at the corneal edge by reason of the presence of a minute abrasion or ulcer of the cornea which, in healing, draws into itself a small fold of adjacent conjunctiva. This makes traction on the latter membrane and starts the growth. A little later other abrasions, from one cause or another, occur near the head of the growth on the cornea, and in healing the head advances still nearer the pupil, becomes large, and the body of the growth becomes wider, thicker, and more vascular, finally developing more or less connective tissue. The unattached wings of the growth furnish a fine culture bed for bacteria, and slight corneal abrasions may easily become infected. This membrane, as a whole, it can readily be conceived is quite capable of making a smart traction on the cornea, quite enough to alter decidedly the relative length of the two principal meridians. Illustrative personal case which demonstrates that a pterygium can and does produce astigmatism. G. P. Hall (Texas State Jour. of Med., Oct., 1911).

TREATMENT.—With irregular astigmatism following keratitis there is always, at first, haziness of the cornea; and probably, remedies for corneal

opacity improve vision partly by lessening irregular astigmatism.

In a few cases **dilatation of the pupil** may improve vision by admitting light through a better portion of the cornea or crystalline lens. **Iridectomy** is applicable in some cases for the same purpose. Contraction of the pupil often makes vision better by lessening the areas of diffusion. Solutions of **pilocarpine**, 1: 500, or **eserine**, 1: 2000, may be instilled for this purpose. Stenopaic spectacles improve vision, but interfere too much with the field of vision to be of much practical value; a horizontal slit is the most practical of stenopaic apparatus. For the mass of cases the correction of regular astigmatism commonly associated with the irregular, and the use of **spherical lenses** that will prevent the straining of accommodation, is the only available optical treatment.

REGULAR ASTIGMATISM.

DEFINITION.—It is the astigmatism that can be corrected by a cylindrical lens.

SYMPTOMS.—It causes the blurring of some or all lines looked at. The eye is able to see with perfect clearness only the lines running in one direction at any one time, although by changing its accommodation it may be able to see clearly lines running at right angles to the first. These two directions, in which lines may be seen clearly, the "principal meridians," may be perceived by the patient, although usually they are only recognized when the eyes are carefully tested. A certain adjustment of the power of accommodation renders lines equally blurred in all directions. Astigmatism may thus cause imperfect vision; but very often the imperfection is only slight and has never been noticed

by the patient. Generally there is some eye-strain, from the effort to focus clearly the lines running in different directions, which all objects present, or to recognize from imperfect retinal images the real form of an object. The symptoms complained of are weakness of the eyes, headache, pain in the eyes on use, inability to use them long, excessive lachrymation, photophobia, nervousness, twitching of the eyelids, and even more serious nerve disease.

Astigmatism usually coexists with hyperopia and myopia, and a portion of the symptoms may be due to one of these. The eye-strain caused by astigmatism is probably a very important factor in the development of myopia.

Many observers believe that astigmatism against the rule, or astigmatism with the meridians placed obliquely, causes more annoyance than astigmatism of the usual form, in which the meridian of greatest refraction is vertical. This latter may be due to the fact that the astigmatic eye can see perfectly only the lines that run in the direction of one of its principal meridians, and that most of the lines which we wish to distinguish are either vertical or horizontal.

Uncorrected astigmatism has been regarded as interfering with the use of various optical instruments. With the microscope only the uses of comparatively low powers are interfered with.

ETIOLOGY.—Astigmatism is caused by a lack of symmetry in the curvature of the refracting surfaces of the cornea or crystalline lens, or an oblique position of such surfaces with reference to the visual line. It does not depend on distortion of the retina. Astigmatism caused by the cornea may be partly or wholly corrected by an opposite astigmatism caused by the

crystalline lens. The wide use of the keratometer (ophthalmometer) of Javal has furnished extended statistics regarding corneal astigmatism, which, by comparison with the total astigmatism of the eye, also indicates the astigmatism due to the crystalline lens.

Extensive wounds or incisions of the cornea give rise to permanent change in the corneal curvature and astigmatism. This is most noticeable after cataract extraction. The astigmatism is highest a few days after the corneal wound has closed, and from then on slowly diminishes until usually within three months, but sometimes later, it becomes stationary. The changes of corneal curvature are flattening of the cornea at right angles to the incision, and increased curvature in the direction of the line joining the ends of the incision.

DIAGNOSIS.—Astigmatism is detected and measured by all of the various methods of determining the refraction of the eye, and should be sought by more than one method in any given case. The chief reliance is to be placed on the keratometer (ophthalmometer), skiascopy, and the test-lenses. Whether it is sometimes corrected by unequal contraction of different parts of the ciliary muscle or is not so corrected, must still be regarded as uncertain.

TREATMENT.—For regular astigmatism the usual remedy is the wearing of **cylindrical lenses**, which should correct the full amount of the astigmatism and should be worn constantly. Any case of astigmatism may be thus corrected by a convex cylindrical lens with its axis placed parallel to the meridian of greatest curvature, or by a concave cylindrical lens with its axis placed perpendicu-

lar to this, or by two lenses of proper strengths with their axes respectively parallel to the two meridians. As may readily be demonstrated mathematically or by trial, the optical effect of any possible combination of cylindrical lenses may be produced by the proper single cylindrical lens combined with the proper spherical lens. By looking obliquely through a spherical lens, a spherocylindrical effect may be obtained, and patients sometimes resort to this when the glasses worn do not fully correct their astigmatism.

The fact that **corneal incisions** change the corneal curvature has suggested their employment for the correction of astigmatism, and where an operation is necessary the corneal incisions may be so planned as to influence favorably the existing astigmatism. The **galvanocautery** has also been suggested for this purpose.

EDWARD JACKSON,
Denver.

ATHETOSIS.—DEFINITION.
—Athetosis (*adæros*, without fixed position) or athetoid movements should be classed as a cerebral affection characterized by slow, deliberate, purposeless, involuntary, more or less rhythmic, and exaggerated movements which are chiefly confined to the hands and feet of one or both sides.

[Although previously observed by Heine and Johannes Mueller in their studies on associated movements, this peculiarly interesting condition was first described, in 1871, by Hammond. A few years later it was studied at greater length, particularly by Clay-Shaw, in England, and Oulmont, in France, and it is to the last-mentioned authors that we really owe our present clear conception of this interesting set of pathological movements. Since then important contributions have been made by Charcot and his followers, Dejerine, Sollier, Arn-

spurger, Audry, Oppenheim, von Monakow, and more recently Lewandowsky. COLLINS AND ZABRISKIE.]

Athetosis occurs usually as a sequela of infantile hemiplegia, although not limited to it exclusively, for even Hammond described 4 cases in which there was no hemiplegia apparent. It has also been observed in epilepsy, idiocy, tabes, and paresis. These are the exceptions, however, and its occurrence, especially in tabetics and idiots, should be accepted with more or less reserve.

We see this condition most often in infantile hemiplegia, as we have said. It is not confined exclusively to this period of life, however, but sometimes, though rarely, develops in adults. While this adult form seems to have been fairly well established, there are some authors (Marie) who insist that it is extremely rare and often confused with hysteric athetoid movements. Lewandowsky also found its appearance in adults to be exceptional, having seen only one case among several hundred hemiplegics. He considers it "an almost specific symptom of hemiplegia acquired in early life."

The muscular movements occur as slow, deliberate, tortuous movements of the hands and feet involving usually the arm as well. They are almost always more pronounced in the arms and hands than in the lower extremities. They are purposeless in character, more or less exaggerated and rhythmic, and, as in chorea, quite involuntary, so that there is a decided inability to maintain the extremities in any given posture. They occur during sleep and are exaggerated by emotional disturbances.

The movements consist usually of flexion of the wrist, with hyperextension of the fingers at the metacarpophalangeal joints. The distal phalanges

are often flexed and the thumb either abducted and extended or adducted and extended. This is the characteristic position of the hand assumed on extension of the arms; that of the foot is a position of equinovarus with the great toe extended. This attitude, which is really the result of an unequal tonus, *i.e.*, an ill-balanced innervation of protagonists and antagonists, cannot be maintained for even a limited period of time, and there ensues the remarkably peculiar muscular activity so characteristic of the condition. A gradual relaxation of the stiff, rigid muscles takes place and a flaccid state appears, or the hand may slowly extend, the arm supinate, and the fingers bend and flex. There is often slow pronation or supination with a moderate rotation of the whole arm. Sometimes there is a slow, deliberate flexion of the first metacarpophalangeal joint, followed by the others in slow succession, the first joint gradually regaining its original posture.

It can readily be seen how many different combinations of movements are possible, and the difficulty of adequately describing them. Once seen, however, they are never forgotten, and the similarity to the moving arms of a polypus to which von Monakow has called attention will be appreciated.

A certain rhythmic quality which becomes apparent if these cases are closely watched is very characteristic. It is marked by pauses of variable duration between the spasmodic muscular contraction, during which the musculature of the affected limbs may be quite flaccid, of normal tonus, or in case of a well-established hemiplegia moderately spastic. This is known as the period of latency.

The effect of exaggerated joint ex-

cursions so striking in many of these cases is produced by lack of proper balance between the protagonists and antagonists. During flexion of the hand, for instance, the extensors are unduly relaxed, whereas in extension of the fingers the flexors release their hold. That it is due to this rather than a mere overactivity of the protagonists is apparently demonstrated by the unequal disturbance of flexion and extension of the different phalanges. On the other hand, if we were dealing with a permanent contracture, the flexion would be more evenly distributed.

In many instances, during the interval between the spasmodic movements, instead of muscular relaxation, there is a definite, constant muscular contraction, fixing the component parts of the extremity in a firmly set position, which is maintained for the same time as the relaxation pauses. This is really a tonic spasm of the muscles, which is known as "*spasmus mobilis*" of the English authors, and manifests itself as the well-known position of flexion of the hand with extension of the fingers so often figured in the textbooks. It is often a very powerful contraction resisting absolutely all voluntary effort on the part of the patient to overcome it, and it can be overcome passively only after a considerable effort. The end of the spasm comes as a relaxation of the tonically contracted muscles, to be followed immediately by the slow, deliberate athetoid movements. This relaxation occurs sometimes rapidly, sometimes slowly, but it almost invariably constitutes the termination of a spasm. The mobile spasm is one of the most constant features of athetosis, in our experience as well as

others (Lewandowsky, Oulmont), and, although it does not occur at every pause, nearly every patient intelligent enough to give correct answers will tell of its appearance at different times. The muscles of the arm and forearm may be the seat of a powerful spasmodic contraction, while the fingers exhibit typical athetoid movements. This latter is often difficult to differentiate from a true hemiplegic contracture, on account of its extreme rigidity and resistance to passive movement. Lewandowsky has called attention to the fact that a true contraction can never be overcome by voluntary innervation to the antagonists because of the blocking of impulses according to Sherrington's theory. The mobile spasm, however, sometimes can be overcome by repeated voluntary effort, since there is no true arrestation of impulses.

The mental state of these patients depends upon the severity of the causative lesion and has nothing to do with the athetoid state itself. It may be complete idiocy, on the one hand, or a perfectly normal mentality, on the other. In other words, the same varied mental state one finds in hemiplegia.

More recently, interest has again been aroused in that form of athetosis to which the name "*athétose double*" has been given by the French writers.

There seems little doubt now that it is a condition quite apart from the posthemiplegic variety and is not merely a bilateral form of the latter. It is of extremely rare occurrence, but possesses several distinguishing features which allow a fairly definite separation from the bilateral form. The condition is almost invariably

associated with other congenital defects, with or without bad heredity, and it is usually acquired in early infancy. There is nearly always some degree of defective intellect, however slight it may be, as well as speech defect varying from a simple dysarthria and aphasia to complete anarthria (Oppenheim). Spastic diplegia is frequently associated with it, although cases have been reported in which there were no spastic phenomena whatever. The chief characteristics of double, or idiopathic, athetosis are: the general distribution of the movements, the face always involved and more so than the feet, the disappearance of the movements during sleep, the combination with associated movements, mobile spasm, and the remarkable manner in which they are increased during excitement or when the attention is directed toward them.

The movements of the face are perhaps the most characteristic of them all. The lips retract slowly, accompanied by wrinkling of the forehead; the eyes are wide open or closed, imparting to the facial expression a peculiar grimacing stare. The features slowly compose themselves and again the same muscular play takes place, now limited to one side of the face, now the other. The head and neck undergo peculiar twisting, rotary movements which often spread over the trunk. The hands, arms, and legs assume the fixed position characteristic of the hemiplegic type, and remarkable postural effects ensue, reminding one greatly of Huntingdon's chorea. There are long quiescent periods when the patient is not excited or aroused emotionally, but the movements are always brought into

play whenever he becomes interested or excited or his attention is directed toward them. The gait, if walking is possible, is characteristic because it almost always brings the entire combination of athetoid movements into play. Walking often provokes mobile spasm in the lower extremities, sometimes to such an extent as to render more than a few steps impossible without support.

[A peculiar flexor spasm of the spine, tending to throw these patients forward and seriously disturb their equilibrium, is rather frequent also. The latter condition was so marked in a little girl of 9 years, recently observed, that she could not walk at all unless supported under the shoulders. This could not have been due merely to a profound degree of spasticity, because when supported as above the patient walked—a fairly normal manner; furthermore, when in the recumbent posture the legs showed an amount of spasm so mild that it could in no way account for the gait without support. Haupt (D. Arch. f. Nervenheilk., 1907, No. 33) has also called attention to this fact, although he does not attempt to explain it. COLLINS AND ZABRISKIE.]

PATHOLOGY.—A glance through the literature on athetosis demonstrates very clearly that there is no particular focal lesion which will produce athetoid movements. Von Monakow has collected about one hundred published cases with autopsy, in which the lack of unanimity of findings is very striking. In about 60 per cent. the lesion was situated in the region of the posterior limb of the internal capsule, *i.e.*, postthalamie region adjoining section of the lenticular nucleus, the optic thalamus, and the retrolenticular region. Lesions have also been found in the corona radiata tegmentum in the vicinity of the red nucleus. The cerebellar hemisphere, the dentate nucleus, and the

peduncles with the substantia nigra. In some instances no lesion at all was found. It seems, however, fairly well established that destructive lesions do not produce this condition, but disturbance somewhere in the pyramidal tracts.

I believe I can do no better than to give von Monakow's theory, namely: That it is a compensatory irritation phenomenon, *i.e.*, continuous compensatory movements. In other words, there is a faulty central division of stimuli passing from the surface to the cortex dependent upon a disturbance somewhere in the pyramidal tracts.

DIAGNOSIS.—Oulmont, in his excellent description of athetosis (*Thèse de Paris*, 1878), insists upon four distinctive features which characterize the condition: 1, the slow, deliberate quality of the movements; 2, the exaggeration; 3, limitation to the hand and foot; 4, transformation into a mobile spasm. We are rather in accord with Lewandowsky, who takes exception to at least two of these in regard to their diagnostic significance. Many authors have described cases in which the athetoid movements were of extremely mild type and only to be seen after careful observation. These movements are also not strictly limited to the hands and feet, for we have observed a slow sinuous twisting of the face in one case and Lewandowsky has twice observed them in the shoulder. Von Monakow also mentions involvement of the face.

The diagnosis of athetosis is usually not difficult if we bear in mind its distinguishing features, *i.e.*, the slow, rhythmic character of the movements and the mobile spasm. These two characteristics are absolutely neces-

sary for the diagnosis of athetosis, and they constitute the principal points of differentiation from chorea (whether it be posthemiplegic, Sydenham's or Huntingdon's), from posthemiplegic associated movements, or from other similar forms. The condition with which athetosis is most frequently confused is posthemiplegic chorea. In the latter the sudden jerky manner in which they begin, the snake-like, twisting character of the movements themselves, their aimlessness, the complete flaccidity during the pauses, and the absence of mobile spasm serve to differentiate it from the former in every instance. Huntingdon's chorea is sometimes mistaken for double athetosis or *vice versa*. But here, again, the absence of all spastic phenomena, the time of life at which it begins, the family history, and mental trouble appearing late in life are characteristic of the former.

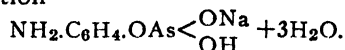
The four distinguishing points given by Oulmont in his well-known thesis, 1, the slow, deliberate quality; 2, exaggeration of the movements; 3, limitation to the hand and foot; 4, transformation to mobile spasm, should really apply only to the hemiplegic form and not at all to the double form, since in the latter only the first and fourth are true.

JOSEPH COLLINS

AND

E. G. ZABRISKIE,
New York.

ATOXYL, or SODIUM ARS-ANILATE, is an organic compound of arsenic having the chemical composition



It may be said to consist of acid sodium arsenate in which one hy-

droxyl group has been replaced by aniline ($C_6H_5.NH_2$). It occurs as a white, crystalline, odorless powder, having a slightly saline taste. It is soluble in 6 parts of water and in approximately 125 parts of alcohol; when left standing a solution of atoxyl in water becomes yellowish. The substance contains about 26 per cent. of elemental arsenic. **Soamin** is a preparation of sodium arsanilate embodying 5 molecules of water of crystallization to each molecule of the arsenic compound. It contains about 22 per cent. of arsenic.

Arsacetin and arsenophenylglycin, substances closely related chemically to atoxyl, will be considered at the close of this article.

DOSE AND MODES OF ADMINISTRATION.—Atoxyl should be used exclusively by hypodermic injection, as when taken orally it is broken down by the hydrochloric acid of the gastric juice. Its dose is $\frac{1}{3}$ to 3 grains (0.021 to 0.2 Gm.) injected on alternate days and gradually increased if required.

PHYSIOLOGICAL ACTION.—The action of atoxyl is essentially that of arsenic, slowed and rendered milder through the fact that the latter is set free only gradually from the organic combination. Atoxyl, while quickly absorbed, is less promptly taken up by the tissues than are the inorganic preparations of arsenic. Its very pronounced effect on the parasites of trypanosomiasis ("sleeping sickness") is believed to occur on this account, *i.e.*, because it remains in the bloodstream a longer period than does inorganic arsenic. Only a relatively small proportion of it is decomposed so as to liberate arsenic in the system,

the greater part of the amount introduced being quite rapidly excreted unchanged in the urine.

UNTOWARD EFFECTS AND POISONING.—The symptoms arising from toxic doses of atoxyl consist of dizziness, headache, tinnitus, deafness, disturbances of sight, vomiting and diarrhea, fever, colic, albuminuria, and partial paralysis of the lower extremities. By far the most important of these possible effects is that on the eyes. So many cases of blindness, usually permanent, have occurred during the use of atoxyl, even in moderate doses for therapeutic purposes, that the drug can by no means be considered a harmless substitute for inorganic arsenic, as some of its sponsors would have had us believe. Thus, Koch in 1902 reported 1633 cases of sleeping sickness treated with atoxyl, with 23 cases of blindness as a result. Schrimmer reported a case of optic atrophy in a patient who had received 52 biweekly injections of atoxyl, amounting altogether to 9.9 grams (McAlester). As Cushny states, the above effects are not those characteristic of chronic arsenic poisoning. Yet, they are probably not caused by the aniline component of atoxyl either, and, since they may appear even after the administration of atoxyl, itself rapidly eliminated, has been stopped, the most plausible explanation is that they are due to the small proportion of inorganic arsenic which is liberated from the organic substance, and that the difference in the toxic effects noted from those of inorganic arsenic is caused by a more widespread penetration of the atoxyl throughout the organism, parts of the latter thus being reached which inor-

ganic arsenic alone would have failed to enter.

Case in which the administration of atoxyl was followed by death. The patient was 28 years of age. There was no history of epilepsy or of alcoholism. Ten weeks after the development of his chancre a maculopapular rash appeared with condylomata at the anus. He was then treated by mercurial inunction for three weeks. A little later he was given 5 grams (77 grains) of potassium iodide daily by the mouth and four injections of 0.1 gram (1½ grains) of salicylate of mercury subcutaneously. After a further interval of six days, during which the patient felt well, atoxyl was given in four separate doses of 0.6 gram (10 grains) spread over a period of eight days. The day after the last injection the patient became seriously ill with malaise, anorexia, vomiting, and sudden rise of temperature. Within a few hours epileptiform attacks supervened, with tonic and clonic spasms and complete loss of consciousness. The pupils were sometimes contracted, sometimes dilated, and insensitive to light. The tendon-reflexes, which were at first abolished, later became exaggerated, and a Babinski reflex was obtained on both sides. Cyanosis supervened, respiration was sometimes deep, at others rapid and superficial, while during the fits breathing would cease for considerable periods. The heart's action became very weak, the pulse rapid and small. The urine contained albumin and casts. Examination of the blood showed a marked leucocytosis and some polycythemia. Death occurred in one of the epileptiform attacks. At the necropsy the heart muscle showed degenerative changes, and there was marked edema of the lungs. The liver showed fatty and necrotic areas, and there were signs of marked destruction of red blood-corpuscles both in the liver and spleen. The kidneys were large, soft, flabby, and congested. In the central nervous sys-

tem the only changes observed were local proliferations of the neuroglia in the cortex and recent degenerative changes in the vessels. Atoxyl is a drug which must be used with great discrimination, and its effects must be very carefully watched. Heinrich Schlecht (Münch. med. Woch., May 11, 1909).

From a study of the literature and a personal case, the writer draws the following conclusions: 1. When there is a marked intoxication with atoxyl, the peripheral endings of the optic nerve are first affected, followed by degeneration of the entire nerve, which stands in intimate relation with the constriction of the retinal vessels. The clinical picture consists of a gradual decolorization of the papilla of the optic nerve, preceded by a marked concentric narrowing of the visual field, particularly on the inner side, followed by constriction of the retinal arteries, and in some cases complete loss of color perception. 2. Atoxyl is markedly toxic to the visual apparatus, even in moderate doses, particularly when administered for a long time. 3. In view of the toxicity of atoxyl, it is necessary to make a careful study of its physiological effects, and to employ great care in its administration. The eyes should be constantly watched, and with the slightest disturbance of the visual field the administration of the drug should be discontinued. Kalashnikoff (Roussky Vrach, Mar. 10, 1912).

Although atoxyl had been given very cautiously by the writer, the patient, a woman of 63, became totally blind after taking 0.725 Gm. (11½ grains) of atoxyl divided in 9 doses in less than 2 weeks. Makrocki (Berl. klin. Woch., Nov. 2, 1914).

Case of almost complete blindness from 1.2 Gm. (18 grains) of atoxyl given over a period of 26 days, for a severe anemia. A study of atoxyl amblyopia led the author to conclude that the toxic action of atoxyl, especially severe and lasting visual disturbances, cannot be excluded even

by the cautious therapeutic employment of the drug. It is especially to be feared when there is latent or obvious disease of the central nervous system, cachexias, autointoxications, chronic infections of the nervous system (lues, etc.), and intoxications, especially chronic alcoholism. These should preclude the use of atoxyl. R. Steinebach (Berl. klin. Woch., June 15, 1914).

The lesion caused by atoxyl where blindness results from its use is an atrophy of the optic nerve,—a phenomenon only very rarely induced by intoxication with inorganic forms of arsenic. Moderation in dosage does not seem to preclude the occurrence of visual disorder, as, while some patients have withstood enormous amounts of atoxyl, atrophy has followed the administration of eight 0.1-gram doses. Ophthalmoscopically there are at first to be seen fine vitreous opacities and narrowing of the arteries; the subsequent progress to complete atrophy may occupy a few weeks to a year or more (McAlester). Examination *post mortem* by Nonne of the optic pathways of a cancer patient treated with atoxyl, blindness resulting, showed parenchymatous degenerative processes in the portion of the optic nerve next to the chiasm as well as in the chiasm itself.

In the optic nerve Marchi's reaction can be obtained with atoxyl, and changes are present characterized by an intense coloration of the neuroglia. Igersheimer (XXXV Versamml. d. Ophth. Gesellsch., Heidelberg, 1908).

Atoxyl amblyopia is the result of optic-nerve atrophy, with primary involvement of the retina, though in certain cases central lesions, shown experimentally and apparent clinically, are very suggestive. B. W. Key (Univ. of Pa. Med. Bull., June, 1909).

Records of 95 cases of disturbance of vision or actual blindness following the use of atoxyl collected. It would seem that the onset of the ocular symptoms is often preceded by some evidence of toxic effects—such as general languor, vertigo, headache, vomiting, colicky pains, dysuria or anuria, hypothermia, tinnitus, and deafness. The ocular symptoms comprise a more or less marked diminution of the power of sight, and the field of vision is concentrically diminished, but more on the nasal than on the temporal side. The ophthalmoscopic examination at first gives negative results save that the retinal arteries may be narrowed, the veins somewhat hyperemic. After a few weeks the papillæ begin to appear pale, and the condition progresses with uncomfortable rapidity to complete optic atrophy, associated with increasing dimness of vision going on to complete blindness. The prognosis of the ocular symptoms is the more grave from the facts that the immediate stopping of the drug does not, as a rule, suffice to stop the progress of the condition, and that treatment has so far proved unsuccessful.

The pathology of the condition is obscure, but it appears to be a simple progressive atrophy. Kurt Steindorff (Berl. klin. Woch., Oct. 3, 1910).

Examination of samples of pure atoxyl kept 3 or 4 years in a tropical locality, showed that it is liable to spontaneous decomposition into highly toxic substances. The decomposition was complete in the samples examined; every 0.5 Gm. ($7\frac{1}{2}$ grains) of atoxyl—a dose commonly given to trypanosomiasis—was changed into 0.03 Gm. ($\frac{1}{2}$ grain) of arsenous anhydride and 0.56 Gm. ($8\frac{3}{4}$ grains) of sodium arsenate. Atoxyl should be examined in the locality where it is to be employed and analyzed before clinical use. François (Bull. de l'Acad. de Méd., Mar. 19, 1918).

The toxic effects observed from use of atoxyl in animals include ataxia

and tremors, particularly in the cat, and renal hemorrhages in the dog. Birch-Hirschfeld and Igersheimer observed in dogs and rabbits which had received small doses of atoxyl for some time destructive processes in the optic nerve, retina, and spinal cord, together with paresis of the bladder and rectum.

Both with acute and chronic atoxyl poisoning in dogs severe hemorrhage into the kidney occurred almost invariably. This is probably the result of a primary effect on the circulatory mechanism of the kidney and not, as some observers state, due to a hemorrhagic nephritis. The hemorrhage occurs between the cortex and the medulla and leads to a more or less extensive atrophy of the parenchyma of the organ. In the cat in subacute or chronic poisoning a train of nervous symptoms is set up consisting in slowness of movement, ataxia, clonic twitchings, and more or less severe spasms and spastic paralyses. The changes underlying these symptoms are found to have their situation in the central nervous system, consisting in severe degenerative processes in the cells of the brain and spinal cord. In both cats and dogs the ordinary symptoms associated with poisoning by inorganic arsenical compounds may be present in addition—viz., inflammation of mucous membranes, conjunctivitis, and trophic changes in the skin. Further experiments with other arsenic compounds seemed to indicate that the symptoms of poisoning by atoxyl are not confined to atoxyl alone, but may occur with other aromatic arsenical compounds. By subacute poisoning with atoxyl no change in the blood-picture is made other than a moderate anemia. The experiments gave no support to the view that the action of atoxyl is due to its aniline or phenyl component. Igersheimer and Itami (Arch. f. exp. Path. u. Pharm., vol. lxi; Lancet, Oct. 16, 1909).

THERAPEUTIC USES.—In trypanosomiasis atoxyl has yielded pronounced beneficial results. Koch, as already mentioned, used it in a large number of cases, and up to 1907 had found no other preparation of arsenic or of any other drug which gave equal results. He injected 0.5 Gm. (8 grains) on two successive days, then allowed ten days to pass, after which he gave two more injections, etc., the treatment being continued in this manner for at least four months. Mild and recent cases were thus cured, though in severe cases recurrences frequently took place after a more or less prolonged interval of freedom from the disease. Increasing the dosage to 1 Gm. (15 grains) at every injection resulted in a number of cases of permanent blindness and had to be abandoned. More recently the tendency has been to use smaller doses; thus, $\frac{1}{2}$ grain (0.03 Gm.), gradually increased to 3 grains (0.18 Gm.), is administered continuously on alternate days, the medication being kept up for a year or more after the parasites have disappeared from the blood. Combination of mercurial treatment with that by atoxyl was shown by Sir Rupert Boyce, experimentally as well as clinically, to be more effective than that by atoxyl alone. It is now recommended to follow the atoxyl medication by a course of mercury.

The manner in which atoxyl acts in trypanosomiasis is not definitely known, though it is generally believed that a direct action on the parasites is exerted. While inorganic forms of arsenic destroy trypanosomes *in vitro*, atoxyl does not act on them very strongly under these conditions. Hence some believe that it is the inorganic arsenic set free from the

atoxyl in the system which possesses the trypanocidal action. According to Ehrlich, however, a product of partial reduction of atoxyl, "trypanotoxyl," which he found strongly trypanocidal *in vitro*, is responsible for the effects, though he has not been able to show that such a partial reduction takes place in the living body.

Experiments on the formation of trypanotoxyl yielded the following conclusions: The organs freed from blood, especially the liver, kidneys, and muscles, have no action on atoxyl; they do not produce a trypanocidal substance. A trypanocidal substance is produced by the red corpuscles of the blood as well as by their solution in water. The red corpuscles washed in physiological saline and treated with carbonic acid, or reduced by the tissues or by different bacteria, have a greater power of producing an active body than the red corpuscles not so treated, and merely washed in saline. Red corpuscles treated with oxygen do not form any active substance. The leucocytes, the blood-serum, the stroma of the red corpuscles, the catalase of the blood, and pure recrystallized hemoglobin are not capable of producing the active substance. Blood dialyzed in water on a collodion membrane or warmed to 80° for thirty minutes loses its power of producing with atoxyl a trypanocidal substance. The active body is soluble in alcohol; it is thermostable and free from proteid matter. The trypanocidal principle combined with the various albumins becomes inactive. *In vivo* after an injection of atoxyl the active body originates in the blood-circulation and afterward combines with the trypanosomes and the other albuminous matters in the blood. T. Yamanouchi (C.-r. de la Soc. de Biol., Jan., 1910).

Whatever be the true explanation of the effects of atoxyl, it is well known that its trypanocidal action soon wears off. Kerandel, who personally took

about 70 grams (2½ ounces) of atoxyl, —without toxic effects of any kind,—believes that the parasites become atoxyl-fast.

In syphilis the use of atoxyl has been highly recommended by Salmon, Curschmann, and Hallopeau. Uhlenhuth found it to exert a stronger protective inoculation against syphilis in rabbits than mercury bichloride. On the other hand, the danger of visual and other complications as a result of its use has become increasingly manifest with the successive reports of clinicians who have used it. In view of the results recently obtained with dioxydi-amidoarsenobenzol, the cacodylates, and other organic arsenicals in this disease, it would hardly seem that there is any field left for atoxyl in the treatment of syphilis.

Atoxyl has been used with beneficial results in a number of affections in which inorganic arsenic preparations had already been availed of. Among these may be mentioned tuberculosis, leukemia, chlorosis, secondary anemias, exophthalmic goiter, malignant tumors, malaria, and frambesia.

Subcutaneous injections of 0.2 to 0.4 Gm. (3 to 6 grains) of atoxyl employed in 18 cases of **pulmonary tuberculosis**. The author is convinced that this remedy, especially when given in full doses, exerts on phthisic patients a curative action much superior to that of cacodylates and other measures commonly employed, including tuberculin. A favorable effect on the pulmonary lesions was noted even where the general nutrition remained uninfluenced or loss of weight actually took place. No untoward effects were noted. Knotte (Russky Vrach, Nos. 30 and 31, 1911; Progr. méd., Feb. 24, 1912).

In a large variety of skin affections, including pellagra, psoriasis, derma-

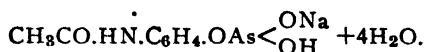
titis herpetiformis, chronic eczema, pityriasis rosea, lichen planus, acñe vulgaris, pemphigus, chronic urticaria, xanthoma, furunculosis, and chloasma, atoxyl has been used with good results.

Sodium cacodylate and atoxyl employed in **psoriasis**. There was improvement, but in no case anything like a cure.

Atoxyl also used with benefit in a severe case of **pemphigus**. Atoxyl, like sodium cacodylate, does not possess any therapeutic properties not possessed by arsenous acid, Fowler's solution, or the arsenate of soda. Its greater solubility and freedom from irritant properties, however, adapt it especially for hypodermic use, a method often preferable to administration by the mouth, and one which usually gives superior therapeutic results. Hartzell (Jour. Amer. Med. Assoc., Oct. 31, 1908).

Fourteen cases of **pellagra**, acute and chronic, in adults and children, were all apparently cured in from six to twenty-eight days by from one to four injections of atoxyl, together with internal administration of 4 mg. of arsenic and inunctions of an arsenical ointment. These results are the more marked because patients frequently suffer from five to twenty years from pellagra, and are transiently improved rather than healed after frequent and long-continued hospital treatment. V. Babes, A. Vasiliu, and N. Gheorghus (Berl. klin. Woch., Feb. 8, 1909).

ARSACETIN is a compound derived from sodium arsanilate (atoxyl) by the replacement of a hydrogen atom in the amino group of the former substance by the acetyl radical. Its chemical make-up is expressed by the term sodium acetyl arsanilate—



It occurs as a white, crystalline body, odorless and tasteless, which is soluble

in 10 parts of cold and $3\frac{1}{2}$ parts of hot water. It can be sterilized by heat without becoming decomposed.

It is used by hypodermic injection in doses of $1\frac{1}{2}$ grains (0.1 Gm.) to $7\frac{1}{2}$ grains (0.5 Gm.), and may also be given internally in doses of $\frac{3}{4}$ grain (0.05 Gm.).

PHYSIOLOGICAL ACTION.—

Arsacetin acts in the same way as atoxyl, but is said to be from 3 to 5 times less toxic to mammals than the latter. According to Ehrlich, who introduced it, arsacetin acts more strongly on trypanosomes than atoxyl.

As regards untoward effects, it appears to be but little superior to atoxyl. Hammes reported 2 cases of blindness out of 142 cases in which injections of arsacetin had been given; he used the drug rather freely, however, injecting, in one of the amaurotic cases, 8 doses of 0.8 Gm. ($12\frac{1}{2}$ grains) each within sixteen days. Eckard reported 3 cases of blindness among 134 cases of sleeping sickness treated with arsacetin, and recommended that it be never given in doses larger than $7\frac{1}{2}$ grains (0.5 Gm.).

Renal irritation appears to be produced with especial facility by arsacetin (Borchers).

THERAPEUTIC USES.—Arsacetin is used for the same purposes as atoxyl and presents the advantage of not being decomposed when sterilized by heat. In **syphilis** the drug has been tried by a number of observers, but its action has been found less trustworthy and less persistent than that of mercury. In **trypanosomiasis** it is considered by Eckard inferior to atoxyl.

Internally, Naegeli and Heinrich have obtained good results with it in **Hodgkin's disease**, and the last-named

observer also in **psoriasis** and **lichen ruber**. Doses of $\frac{1}{2}$ to $\frac{3}{4}$ grain (0.03 to 0.05 Gm.) three or four times daily were used and no untoward effects observed.

In the **recurrent fever** prevalent in Russia Iversen employed the drug with satisfaction in 100 cases; $7\frac{1}{2}$ grains (0.5 Gm.) were injected every second to fourth day.

In **pernicious anemia** Klemperer obtained excellent results by administering subcutaneously 2-grain (0.12 Gm.) doses of arsacetin (in a 10 per cent. solution), gradually increased to 10 grains (0.65 Gm.) in some cases.

ARSENOPHENYLGLYCIN is another of the organic arsenicals or aryl-larsonates recently introduced into therapeutics by Ehrlich. Its composition is $\text{NaOOC} \cdot \text{CH}_3 \cdot \text{HN} \cdot \text{C}_6\text{H}_4 \cdot \text{As} = \text{As} \cdot \text{C}_6\text{H}_4 \cdot \text{NH} \cdot \text{CH}_3 \cdot \text{COONa}$, and it occurs as a yellow powder, which is readily soluble in water. Different from arsacetin, it decomposes rapidly when left in contact with the air, and must therefore be kept in sealed tubes.

The preparation has so far been used chiefly in **trypanosomiasis**. Zupitza and von Raven injected as much as 12 to 15 grains (0.8 to 1.0 Gm.) at a dose in early cases, and claim that it gives better results than atoxyl. They do not advise its use in advanced cases, however, as repeated injections would be required, and the compound proved dangerous when given repeatedly, even in divided doses. The reason for this was later supplied through the researches of Fischer and Hoppe, who showed that, while arsacetin is eliminated by the urine in two days, and atoxyl in three days, arsenophenylglycin remains in

the organism for six to eight days, accumulation in the system thus occurring much more readily with the latter substance. Alt treated 31 cases of **general paresis** with intramuscular injections of arsenophenylglycin; the Wassermann reaction became negative in 7 instances.

C. E. DE M. SAJOUS

AND

I. T. DE M. SAJOUS,
Philadelphia.

ATROPINE. See **BELLADONNA**.

AURICULAR FIBRILLATION.

See **HEART AND PERICARDIUM, DISEASES OF**.

AUTOINTOXICATION AND ACIDOSIS.—These two conditions being more or less merged pathologically, they are considered separately to establish clearly their etiological difference.

AUTOINTOXICATION.

DEFINITION.—Although various disorders may give rise to autointoxication, the form treated herein is that usually meant by the term, viz., intoxication due to poisons absorbed from the gastrointestinal canal.

The writer deems it more rational to attribute the evil effects of intestinal stasis to conditions favoring subinfection and low forms of infection than as a result of chronic intoxication. He considers the term "gastro-intestinal autointoxication" as pernicious. While he deems it possible that the symptoms and diseases enumerated by Lane may follow intestinal stasis, he is convinced at least a large proportion of them may originate independently of such stasis. Before recommending the operation of short-circuiting it is necessary, therefore, to make the fullest studies, so as to discover, if possible, the

nature of the organism responsible for the disturbance and its probable seat of entry. A discovery of the cause of the symptoms is calculated to suggest methods of treatment other than short-circuiting. Only when these have been tried and found wanting is removal or short-circuiting of the colon justifiable. J. G. Adami (Brit. Med. Jour., Jan. 24, 1914).

PATHOGENESIS.—Were all food products admitted to the digestive tract submitted to complete digestion and the end-products of the process absorbed by the intestinal mucosa fully prepared, in the physiological sense, for this process, autointoxication of intestinal origin would never occur. But such is not always, and is probably seldom, the case. Some observers have estimated that one-tenth and others one-seventh of the food we ingest fails to be acted upon by the intestinal digestive ferments. Were this undigested fraction at once eliminated per rectum it would cause no trouble; but such not being the case, it is retained sufficiently long in the intestine to putrefy, *i.e.*, to be broken down by bacteria, particularly the putrefactive anaërobes, aided by the colon bacillus. It is the product of this putrefactive process which, absorbed in sufficient quantity and passing into the blood, causes the phenomena of autointoxication.

Carbohydrate decomposition due to the action of bacteria occurs mainly in the stomach and small intestine, while proteid putrefaction occurs mainly in the large intestine.

Emphasis must be laid upon the fact that it is when certain quantities of these toxic products of putrefaction reach the blood that these phenomena occur, since, as stated above,

a small proportion of the foodstuffs ingested undergoes putrefaction under normal conditions. But the body is protected in two ways from the injurious effects of these poisons: (1) by the detoxicatory functions of the liver, which organ the poisons must traverse before they reach the general circulation, and (2) by the antitoxic constituents or antibodies in the blood proper, of which the poisons provoke an increased production by acting as antigens.

Autointoxication is usually attributed to dietetic errors, the use of meat in excess, gorging, etc., but, as the above facts suggest, *three* factors should be taken into account: dietetic errors; the efficiency of the liver, and finally the autodefensive activity of the blood.

Anesthesia also gives rise at times, especially in children, to acidosis, the most characteristic symptoms of which are intense thirst, vomiting, restlessness, and finally coma. Air-hunger has been observed in some cases. See ACIDOSIS in the first volume.

From a surgical standpoint, it is necessary to include under autointoxication not alone the lesions caused by substances formed through the vital processes of the organism, which is Coombe's conception, but also those arising from destructive infection of the bowel wall, which in a sense is not true autointoxication, but essentially a surgical disease. Surgeons can at present do no better than to find a means to prevent the absorption of the toxins from a given part of the bowel, however these poisons may have been created. Most acute and chronic purulent colonic infections are surgical from the start, and the future functional efficiency of the organ and of the individual depends on early recognition and proper treatment. Acute strepto-

coccic embolic septic colitis, chronic torpid ulcer, slowly progressive colitis and acute diphtheroid hemorrhagic colitis yield only to surgical therapeutics. J. W. Draper and J. M. Lynch (Jour. Amer. Med. Assoc., May 22, 1915).

It is not sufficient to show that toxic substances can be formed during the bacterial destruction of nitrogenous matter; it must be demonstrated that these toxins are formed in the intestine, that they can pass through the mucous membrane, that they can escape destruction by the liver and reach the general circulation in amounts sufficient to produce symptoms, and that the symptoms produced by the repeated injection of small doses of these substances into animals are similar to those observed in constipated man. Moreover, the greatest care should be exercised in drawing conclusions from results of experiments *in vitro*, as it seems clear that in the bowel antibacterial forces are at work. It should also be remembered that nearly all the bacteria found in feces are dead, that organisms cannot multiply in constipated feces on account of the dryness and lack of nitrogenous food, and that the great number of intestinal bacteria produce no soluble toxins. Furthermore, absorption cannot take place unless the feces are liquid and churned actively to and fro, whereas the Röntgen ray has shown that the feces begin to harden in the ascending colon and thereafter undergo no churning movements. The fact that the usual symptoms of the constipated disappear so promptly after a bowel movement proves that they cannot be due to absorbed toxins, and they must therefore be produced by distention and irritation of the colon. Such symptoms occur in nervous people, in whom the brain is profoundly influenced by afferent impulses from a distended, overactive and wrongly acting bowel. Many symptoms of constipation are due simply to plugging of the lower end of the canal,

which slows or stops the downward current and produces ripples of reverse peristalsis, which run up the bowel and break into deeper waves in the upper part of the stomach and esophagus. In this way, more than the usual amount of bile is carried back into the stomach and up into the mouth, leading to biliousness, lack of appetite, feeling of fullness after eating a few mouthfuls, coated tongue, etc. The relief experienced after taking calomel is due to restoration of the normal downward currents. Overwork, worry and lack of sleep may also give rise to symptoms attributed to autointoxication, and finally to constipation. In short, nervousness is generally the cause and not the result of constipation. W. C. Alvarez (Jour. Amer. Med. Assoc., Jan. 4, 1919).

SYMPTOMATOLOGY AND DIAGNOSIS.—

In identifying a case of true autointoxication it is necessary to eliminate other possible disorders. The toxemia may be due to quite another cause, *i.e.*, deficient catabolism of waste products with an accumulation of purin bases in the blood, in other words, the gouty diathesis, often merged with autointoxication of intestinal origin. Imperfect elimination of end-products also complicates chronic nephritis long before the stage of uremia appears. The accumulation of acetone or diacetic acid in the course of diabetes is another form of toxemia for which intestinal autointoxication might be mistaken. This applies also to hepatic torpidity due to cholangitis; gall-stones, even though they may not, as yet, have produced biliary colic; incipient hepatic cancer, and appendicitis attended by gastrointestinal disorders. Intestinal entozoa may also awaken symptoms simulating autointoxication.

The presence of this condition being determined, it is desirable to ascertain which of three underlying causes predominates. While the high liver or individual who eats meat in excess may be ruddy or even appear congested, he will complain of symptoms similar to those described above that would occur in a pale, fallow woman. In the former, the morbid phenomena will be due to excess of proteids over and above his ability to digest them and destroy the poisons in the blood-stream, though, perhaps, both his digestive and antitoxic powers be normal. In the pale woman, on the other hand, both these functions may be deficient and even a small quantity of protein suffice to bring on the symptoms of autointoxication because of the large relative proportion of protein which undergoes putrefaction. The third patient may appear muddy, yellowish and fat, or emaciated—a type often due to hepatic torpor or incipient renal disease of toxemic origin. This shows that the general appearance of the patient is not typical of the disorder, though it affords a clue to the underlying cause.

Headache, often frontal and extending to other parts of the head, finally becomes a true hemicrania; it is sometimes migratory, *i.e.*, moving about from one place to the other. It may be continuous both day and night or recur at fixed intervals, sometimes once or twice a week. The face is apt to be pale during these headaches; there may also be vertigo, considerable lassitude, and, perhaps, nausea. During the intervals, the patient often complains of anorexia, dyspepsia, borborygmus, flatulence, with more or less stubborn constipa-

tion or, rarely, diarrhea. There may be insomnia, or, even if the patient sleeps, fatigue on rising, and drowsiness during the day. Palpitations or arrhythmia and dyspnea on exertion and a stubborn cough are not infrequent, and the sufferer is often irritable. The blood-pressure, excepting in the habitually weak and anemic, is usually high, ranging from 150 to above 200.

When the blood-pressure is very high, however, a renal disorder is apt to be present. Although the urine may prove negative, some severe cases of long standing may show albumin, and also sugar, both of which disappear under appropriate treatment. Debility and emaciation, melancholia and hypochondria, are not uncommon, especially when the paroxysms of headache, the cardinal symptom of the disorder, are frequent and severe. Children are apt to suffer from periodical attacks of fever, which promptly disappear under the influence of a purgative.

Cutaneous disorders, especially eczema and acne, are not infrequently observed. Occasionally there is flushing, icterus, and urticaria. Blood anomalies, chlorosis and anemia, are occasionally noted, especially in females. Various neuroses have been attributed to the same cause; these are treated under their respective heads. A number of eye affections have also been ascribed to autointoxication of gastrointestinal origin.

TREATMENT.—In this disorder dietetic measures are of primary importance irrespective of the class—the three referred to above—met with. The main indication is to diminish the proteids ingested, *i.e.*, **reduce meats** especially, to just within the

limits of proper digestibility. In some cases nothing short of **complete meat abstention** suffices; in others it may be allowed from once to seven times a week, *i.e.*, once daily. The **antiputrefactive diet** should then be adjusted to supply daily from 60 to 75 grams (2 to 2½ ounces) of protein and, from 1800 to 2500 calories (*vide* Dietetics) of fuel value. This diet may be made up mainly of milk, one quart daily; milk soups, bread and butter, cereals, fat bacon, cream cheese, vegetables, fruits, especially bananas; honey, salads, olive oil, and fresh cheese. **Soured milk, curdled milk, whey, and buttermilk** are valuable. Metchnikoff's **bacillac** or **lacto-bacillin** are likewise useful by acting directly on the intestinal flora. Weak tea or coffee may be allowed.

Some patients bear fish without trouble, while any kind of meat, even fowl, will provoke autointoxication phenomena. Fish, poultry, and eggs might be continued once daily each, and only suppressed in turn if these untoward effects continued after the withdrawal of meat, for white of egg also undergoes putrefaction. Constipated individuals should eat copiously of vegetables to provide the intestines with cellulose, which facilitates evacuation mechanically.

While putrefaction of proteids occurs mainly in the colon, we have seen, carbohydrate decomposition occurs in the stomach and small intestine. Cane-sugar is the offending agent in the majority of these cases, especially when used in exaggerated quantity. Hence, **reduction of sugar and sweets** is often an important feature of the treatment.

The treatment should be directed against any existing infectious agent,

but reliance should not be placed upon the Bulgarian bacillus as a corrective agent. Cathartics should be avoided. An initial radical change should be made in the **dietary** in an attempt to change the bacterial flora. The colonic function must be restored by regulation of diet and physical means, at times by surgical procedure. Soper (Trans. Amer. Med. Assoc.; N. Y. Med. Jour., June 9, 1917).

Constipation should be met by salines, preferably **magnesium sulphate**, 1 or 2 teaspoonfuls in a glass of hot water on retiring. Colonic irrigation with **saline solution** two or three times a week is very efficient. In some cases the most satisfactory measure is to inject **olive oil**, 4 ounces (120 c.c.), in the rectum on retiring; kept in all night, this insures a free passage by morning. **Castor oil** is the best agent as an occasional purgative in children.

In most cases, especially those attended by debility, pallor, and anemia, **thyroid gland**, 1 grain (0.065 Gm.) during meals, enhances greatly the antitoxic power of the blood. In women this may be advantageously combined with **ovarian extract**, 2 grains (0.13 Gm.).

Where anemia is present **spinach** should form a daily article of diet, owing to its wealth in organic iron, or **Blaud's pill**, 2 grains (0.13 Gm.), and **strychnine**, ⅓ grain (0.0011 Gm.), may be given as chalybeate and tonic. In some cases the curative process is aided by intestinal antisepsis. This is best obtained with **salol**, 5 grains (0.32 Gm.) after meals, or **creosote carbonate**, 5 grains (0.32 Gm.) in capsules in the middle of each meal to prevent the anorexia and gastric disturbance the latter agent some-

times causes. A liberal intake of **fresh water**, though not during meals, and **out-of-door exercise** are beneficial adjuncts.

In cases of hepatic torpor **calomel** is very useful, especially when 1 grain (0.065 Gm.) is given in six divided doses thirty minutes apart followed by a Seidlitz powder. This given once or twice a week serves to keep the liver, and the flow of bile, which contributes markedly to intestinal antiseptics, sufficiently active in cases **unattended** by hepatic organic lesions.

The dyspnea met with in these cases is clearly due to meat, since aggravation is caused by increasing the latter, while the symptom disappears when the patient is placed on a milk diet. It is evidently due, as suggested by Huchard, to vasoconstriction (of the arterioles), for the pallor which accompanies the dyspnea likewise ceases. If slight edema is present **theobromine** is indicated to enhance the functional activity of the heart and kidneys.

ACIDOSIS, OR ACID INTOXICATION.

The body protects itself against the morbid influence of these acids in three ways: (1) Acids displace carbonic acid from the sodium bicarbonate and sets carbonic dioxide free. The latter is then removed by increased pulmonary ventilation—hyperpnea, *i.e.*, increase of respiratory movements or exchanges, leaving a neutral sodium salt (oxybutyrate, chloride, etc.), which the kidneys can readily eliminate. (2) Elimination of the acid, as shown by the ability to excrete an acid urine when the blood is nearly neutral. (3) The production by the body of an alkali ammonia, capable of neutralizing the acid. Van Slyke (*ibid.*) emphasized the fact that acidosis may also be caused, not only by an overproduction of acids, but also through retarded elimination of them.

The writers studied on 10 boys the effects of acid-producing diets and were led to the conclusion that the response to such a diet is a variable factor. In a general way the increase of acetone bodies in the blood was found proportionate to the severity of the acidosis. The glucose content of the blood was examined in 8 cases; of these, 6 showed a decrease during the period of acidosis; 2 did not. Sawyer, Stevens and Baumann (*Amer. Jour. Dis. of Child.*, Jan., 1918).

Etiology.—We have seen under Acetonuria that acetone acidosis was due in children to the excessive consumption of fats, cream, etc. In true acidosis, as stated above, and as Bassler (*Amer. Med.*, June, 1916) words it, we are dealing "with decreased alkalinity of the blood." This is usually due in normal children to a diet in which basic salts, such as those supplied by vegetables, cereals, citrus fruit, etc., are too scant. Such children show as prominent symptoms recurrent vomiting and hyperpnea, or exaggeration respiration without cyanosis, as shown below. It is also, as is well known, commonly observed in diabetes, and in infantile diarrhea.

Pregnancy may also give rise to acidosis, probably owing to the excessive use of the maternal basic salts by the fetus. W. S. Gordon (*N. Y. Med. Jour.*, Mar. 15, 1913) warns that one should be especially on the watch for a toxemia from this source not accounted for by kidney involvement or the retention of urea lest grave and unsuspected complication develop.

The toxemias of pregnancy cannot be attributed, however, according to Losee and Van Slyke (*Bull. Lying-in Hosp. of City of N. Y.*, Jan., 1917), to failure of diamination of the amino-acids, nor to the moderate degree of acidosis observed. The nature of the toxin or toxins therefore remains unknown. Again, A. Hunter (*Can. Lancet*, Feb., 1917) states that among nephritic cases there seems to be no relation between the degree of the acidosis and the severity of the dyspnea. It would seem that in cardiac cases without renal involvement the dyspnea is due

to several different causes, including acidosis, obstruction to the gaseous exchange in the lungs, and hyperexcitability of the respiratory center.

In a study of 68 normal pregnancies, however, L. A. Emge (Amer. Jour. of Obstet., Nov., 1916) found, with the aid of 4 tests, that acidosis was present in the great majority of instances. In view of his results he suggests hesitation in drawing conclusions as to its significance.

Many other disorders, medical and surgical, may also cause acidosis. Thus Crile (Trans. of the Med. Soc. of the State of New York, Apr. 26 to 29, 1915), in enumerating the conditions in which it occurs, mentions the fatigue of the athlete, Graves's disease, fever, emotions, cyclic vomiting, Bright's disease, surgical shock, anesthesia by ether, chloroform, nitrous oxide, toxemias due to intestinal stasis, asphyxia, starvation, diabetes, and other conditions. These are regarded as activators of energy transformation through the adrenals which they stimulate, causing an abnormal output of adrenin, thereby increasing respiratory activity and oxidation, and leading to an increased production of acid by-products.

[This generalization is too broad. We doubtless have increased oxidation and metabolism as a result of an increased output of adrenin (roles which, by the way, my own labors first pointed out), with the co-operation, I would add, of the thyroid secretion. We cannot, however, attribute *all* the forms of acidosis mentioned to this process. Thus, cyclic vomiting, shock, starvation, deficiency of carbohydrates, and other conditions are not promoters of "excessive kinetic activations," as Crile words it, but rather of the reverse, *i.e.*, of disorders in which oxidation and metabolism are slowed. When such is the case, the normal balance between the acids and bases (mainly sodium bicarbonate) in the plasma is disturbed, and acids accumulate in the blood (acidemia) *passively*, *i.e.*, owing to deficient catabolism and elimination of their end-products. Indeed, from my viewpoint, we should recognize, with the ductless glands as participants in the etiological process, at least three general types of acidosis:—

1. *Passive acidosis due to deficiency of basic salts*, mainly sodium bicarbonate, as in recurrent vomiting, due to foods lacking in basic salts, infantile diarrhea with acetone breath (acetone here because the food administered is rich in fats, such as those in cream, rich milk, butter, etc.), starvation, gastric ulcer, diabetes with acetone breath (due to deficiency of lipase), surgical shock, cardiovascular lesions in the aged, for example.

2. *Active acidosis due to overproduction of acids* as wastes in the course of excessive metabolism, as in violent exercise, athletics, intense mental excitement or labor, pregnancy, etc.; or produced as a result of abnormal autodefensive activity, as in acute fevers. Graves's disease of toxic origin, toxics of intestinal origin, chloroform, ether, cancer, hepatic and gastrointestinal disorders of an adynamic type, autoinfections of tonsillar, gingival and nasal origin, etc., in all of which the ductless glands are overactive.

3. *Obstructive acidosis due to renal, intestinal and cutaneous disorders* in which the elimination of acids is inadequately performed or arrested, as in Bright's disease and other organic disorders of the kidney, nephrectomy, constipation, extensive burns, etc., causing not only retention of acids with other wastes, but increasing the activity of the ductless glands as factors of the defensive mechanism, thus still further augmenting wastes including various acids.

The importance of discriminating between these three classes asserts itself especially when the therapeutics of acidosis is in question. C. E. DE M. S.]

Symptomatology.—The salient symptoms of acidosis due to *miscellaneous causes* are hyperpnea, or increase of respiratory movements, the purpose of which is to hasten the elimination of the acid, sighing respiration, nausea, and, in severe cases, vomiting, which may be brought on by the mere act of swallowing and a sweetish apple-like odor of the breath. All these symptoms are, of course, in addition to those of the causative disorder.

In *diabetes* a severe degree of acidosis, which may occur irrespective of any suggestive indication in the urine, may give

rise to headache, vertigo, faintness, somnolence, nausea and vomiting, and hyperpnea, or air-hunger, besides the peculiar apple-like odor of the breath. These symptoms should be taken jointly as danger signals of impending diabetic coma.

In children *intermittent vomiting* is commonly observed, the attacks recurring usually every three or four weeks in most instances. It is mainly observed in high-strung, nervous and hypersensitive subjects. Besides the sweetish breath, there may be dryness of the tongue, mouth and pharynx, and thirst. Fever, ranging from 102° to 104° F. (38.9° to 40° C.), may develop. In mild cases such an attack may occur after dietetic indiscretion, particularly in children that have been subjected to a diet mainly composed of milk, and other foods in which basic salts are scant.

In the more severe cases, as stated by Louis Fischer (Amer. Med., June, 1916), a stuporous or even semicomatose condition and marked fever may appear. The eyes seem sunken and have dark circles about them. A typhoid state with profound toxicity, or meningitis, may be suggested. Vomiting is pronounced and marked by the slightest quantities of food or fluid ingested. Abdominal and gastric tenderness may be such as to suggest appendicitis. Edema and icterus may also appear. Examination of the urine in such cases indicates a large quantity of acetone, traces of albumin, and traces of diacetic acid. Howland and Marriott (Jour. Am. Med. Assoc., Jan., 1916) refer to a diminution of the output of urine as striking evidence of acidosis in infancy.

A form of acidosis associated with certain *intestinal disorders* was observed by Chapin and Pease (Trans. Amer. Med. Assoc., June 17, 1916). Many of the children did not show acetone or diacetic acid in the urine, and the illness was out of all proportion to the symptoms. The children became cyanotic, then stuporous, finally coma supervened. The tongue was sometimes coated and had a red margin. The temperature was not high except when death was approaching, when it rose to 104° F. (40° C.) or more in some. What vomiting there was ceased as the stupor and coma came on.

In a study of the relationship between

acidosis with diarrhea in 200 infants. Schloss and Stetson (Amer. Jour. Dis. of Children, Mar., 1917) found that those suffering from severe diarrhea with toxic symptoms often show the following signs of acidosis: 1, decrease of the carbon dioxide of the blood and alveolar air; 2, decreased carbon dioxide combining power of the blood plasma; 3, high ammonia coefficient in the urine; 4, increased tolerance to sodium bicarbonate; 5, improvement of the symptoms after administration of sodium bicarbonate. These signs are evident in some cases of diarrhea before the typical symptoms of intoxication have developed, and serve as a warning and therapeutic indication. If an infant suffering from severe diarrhea has hyperpnea, the diagnosis of acidosis is almost certain. If hyperpnea is not observed the diagnosis of acidosis must rest on laboratory evidence.

A form following *weaning* was described by Abt (*ibid.*). At first there were vomiting and diarrhea, and, later, rapid breathing, pallor, and obstinate constipation. The urine contained tyrosin and leucin, as well as acetone and diacetic acid. He observed 3 cases in one family, and states that the third child was saved by treatment with glucose and sodium bicarbonate.

J. L. Morse (*ibid.*) refers to cases following *bacterial infection*, general or originating from a local focus, in children. In most instances the only symptoms observed were vomiting, increase of the respiratory excursions and diminution in the amount of urine. Large amounts of acetone bodies were found in the urine. Some of the cases proved fatal.

The multiplicity of factors which may produce acidosis is well shown by cases reported by E. Cecil Williams (Brit. Jour. of Dis. of Children, Nov., 1915), some of which were due to *toxic foods*, including mussels and ice-cream. The cases, all in children, presented symptoms suggesting meningitis, but an examination of the cerebrospinal fluid proved negative.

Diagnosis.—The information afforded by acetone tests is unreliable in the sense that acidosis may be present and acetone fail to appear in the urine. A negative acetone test affords, therefore, no diag-

nostic information. The clinical signs of acidosis, however, plus simple office tests, are virtually conclusive.

[Thus, even if acetone tests fail, we have (1) hyperpnea, or air-hunger, and inability to hold the breath (*vide infra*) more than 30 seconds; (2) and the **methyl-red test** (the *solution*—available at chemist's), 1 drop of which, on filter-paper wet with the urine (avoiding ante-breakfast urine), turns it red, thus indicating acidity (which would be yellow if the urine were alkaline), acidosis is undoubtedly present. If besides these signs there is recurrent vomiting the acidosis is severe. The degree of severity may be gauged by dropping on the same wet paper *para-nitro-phenol*. If the urine is alkaline or weakly acid, the spots will turn yellow with a tinge of green; if strongly acid, no change of color will be noticed, thus indicating a strongly acid urine and intense general acidosis. Or, a drop of *dilute phenolphthalein solution* in a sample of urine will turn it pink or crimson if alkaline, according to the intensity of the alkalinity, but if acid no change of color will be observed. Litmus-paper is useless, and often misleading. C. E. DE M. S.]

Again, the presence of *betaoxybutyric acid* in the urine may prove of diagnostic value, for it never occurs normally. It is often associated with acetonuria and diacetonuria in diabetes, sometimes in fever, and is believed by von Jaksch, to be the immediate cause of diabetic coma. Simon states that the excretion of more than 25 grains of *betaoxybutyric acid* indicates impending coma. Diacetic acid is usually formed first, then acetone and *betaoxybutyric acid*. Its presence may be ascertained in various ways. Among these may be mentioned the **polariscope test**. If a urine be levorotary after fermentation with yeast, it is strongly probable that this acid is present. This may be confirmed by means of **Kulz's test**. After fermenting the urine with yeast it is evaporated to a syrupy consistence. An equal volume of concentrated sulphuric acid is then added and the mixture distilled without cooling; *alpha-crotonic acid* is produced, which is distilled and, after strongly cooling, the distillate is collected in a glass. Crystals

which melt at 72° C. separate. If no crystals be obtained, the distillate should be shaken with ether and the melting point tested with the residue, which has been washed with the water obtained after evaporating the ether. (See also the article on ACETONURIA, in the present volume.)

An important addition to our means of detecting acidosis is **Marriott's alveolar air test** (Jour. Amer. Med. Assoc., May 20, 1916), essentially that of Plesch, as modified by Higgins. It is based on the fact that in acidosis the concentration (tension) of the carbonic acid in the air-cells is diminished. The degree of tension corresponding with that of acidosis, the severity of the latter may be determined. The air (about 600 c.c.) is blown without effort by the patient in a rubber bag about 1500 c.c. capacity. The air thus collected is then run into a solution of 1:100 normal alkali and phenolphthalein, and the resulting color is compared with the graded colors of the contents of a set of tubes which colors correspond with known quantities of carbonic acid in air. (See original article for details concerning necessary equipment.) The normal carbonic acid tension of an adult being 40 to 45 mm., the test may indicate it to be 30, 25 or 20, usually the lowest limit reached, and which indicates imminent danger. In coma it may reach 10 mm. In infants the normal tension is from 3 to 5 mm. lower than in adults.

P. Roth (Jour. Amer. Med. Assoc., July 31, 1915) uses the **Haldane test**, but secures two samples, both taken alike from a complete expiration following a normal inspiration. The patient breathes through a glass tube into a test-tube containing a few c.c. of alkaline solution of mercuric cyanide and silver nitrate. Acetone gives an opalescent precipitate and is reported simply in terms of "trace," "plus," etc. For collecting samples from patients who are unconscious or from those who cannot co-operate, the following method is satisfactory: The subject breathes normally back and forth for 25 seconds into the same collecting tube used in the Haldane method, with the valve turned so as to connect the patient from the start with the rubber tube. At the end of the period,

and as nearly as possible at the end of an expiration, the valve is turned to seal the sample obtained in the rubber tube, from which it is transferred at once into the sample buret. With normal carbon dioxide tension in the alveolar air there is no appreciable acidosis *even with acetone perceptible in the breath*. This means the border line of acidosis, however. A tension below the minimum normal indicates an acidosis proportional to the fall of tension, and tension of 15 to 20 mm. indicates threatened coma. In coma the tension may go as low as 5 or 6 mm. or less until death, when it falls to 0.

Finally, Y. Henderson (Jour. Amer. Med. Assoc., July 25, 1914), found that *inability to hold the breath* at all is a sign of acidosis in its acute stage. The normal period is between 30 and 40 seconds; any period under 20 seconds indicates acidosis.

Iodine Urine Test.—To 145 c.c. of water (hydrant water will do) are added 3 c.c. of Lugol's solution and 2 c.c. of a saturated solution of picric acid, the whole being thoroughly mixed. The result is a fine clear reddish liquid of bright color. Pour this liquid into a white dish and heat it on the water bath to a temperature of 180° F., but if a water bath is not available it may be heated over the flame until fumes are abundantly given off, boiling being avoided by turning down the flame sufficiently. When thus heated, the urine is added as quickly as possible but in small amounts at a time, using for this purpose a graduated buret. In acidosis the amount of urine needed to turn the bright red color to a bright yellow color is small, and the smaller the worse the case. In severe cases 2 or 3 c.c. of urine will almost immediately discharge the red color. In cases of moderate severity 8 or 10 c.c. may be required. Mitchell (Med. Record, Mar. 8, 1919).

Prophylaxis.—In *surgical acidosis* prophylactic measures are increasingly being employed. W. B. Russ (Jour. Amer. Med. Assoc., Nov. 1, 1913) holds that many patients suffering from acidosis are unfit subjects for general anesthesia and the

ordeal of an operation. The warning signs in such cases are: (1) A history of unaccountable headaches, vertigo, attacks of dyspnea, occasional nausea or vomiting, an unreasonable dread of the operation, tachycardia, and other nervous symptoms. (2) A peculiar sweetish odor to the breath, suggesting the odor of decayed apples. In some cases this is marked and unmistakable. (3) The presence in the urine of the acetone bodies. Referring to the influence of peripheral irritations as a cause of acidosis through the adrenals or chromaffin system, R. T. Morris (Amer. Med., June, 1916), advocates the removal of such conditions as eye-strain, nasal hypertrophies, loose kidneys, hemorrhoids, etc., to enable such patients to withstand the effects of severe surgical work.

Referring to the influence of acidosis on surgical procedures, Lincoln (Annals of Surg., Feb., 1917) urges that surgeons should bear in mind the danger in the preparation of patients for operations of a too prolonged starvation, especially in the case of children or those suffering from any form of exhaustion.

As to preoperative prophylaxis, in 138 consecutive major operations, Quillian (Annals of Surg., Apr., 1916) had no mortality and but 5 cases of shock by resorting to the following prophylactic routine: **Sodium bicarbonate** 3ss (2 Gm.) in one-half glass of water *t. i. d.*, one-half hour before meals, for two days preceding operation. The same salt and **glucose** āā 3ss (15 Gm.) with water *q. s. ad* 3viij (210 c.c.) as a retention enema, *b. i. d.*, for two days preceding operation. **Liquid diet** and large quantities of water for 48 hours preceding operation, but no butter-milk or egg-albumins for 24 hours.

The morning preceding the day of operation castor oil 3ss (15 Gm.). **Soapsuds enemata** the night preceding, and the morning of, the operation. **Strontium bromide** gr. xxx (2 Gm.) the night preceding operation to insure a good night's rest. **Morphine**, gr. ¼ (0.008 Gm.), with **scopolamine**, gr. ¼₁₀₀ (0.0006 Gm.), one hour preceding gas and ether anesthetic.

After operation **sodium bicarbonate**, 3ss (2 Gm.), in one-half glass of water one-half hour after meals for several days. **Water and liquid diet** as soon as nausea

ceases, and continued until a light diet is begun on the fourth day. An **eliminant** on the third day after the operation.

Treatment.—In its general lines the indications, besides that of the causative condition, are as stated by McLeave (Jour. Amer. Med. Assoc., Nov. 15, 1913) in the *acidosis of children*, a dietary low in fats with ample amounts of carbohydrate. Citrus, fruit juices, and grape juices are also valuable. Fatigue and undue excitement should be avoided. **Sodium bicarbonate** in 1- to 2- dram (4 to 8 Gm.) doses weekly, and periodic emptying of the large bowel tend to abort the attacks. During the attack sodium bicarbonate can be given in 60-grain (4 Gm.) doses every 3 or 4 hours by mouth or rectum. **Sugar** must be given, preferably dextrose, in 4 per cent. solution with alkali, either by mouth or rectum. **Saline infusions** are given to counteract the loss of fluids by the excessive vomiting; and **opium, chloral**, and the **bromides** to control the nervous manifestations. Blodgett (Amer. Med., June, 1916), who first called attention to the connection between persistent vomiting and acidosis, found that the best way to administer **sodium bicarbonate** was to inject a pint of normal saline solution containing 40 grains (2.6 Gm.) of the salt intramuscularly over the scapula. This can be repeated over the other scapula within an hour. The salt can also be given orally, but experience has caused other observers to discard this method when free emesis occurs. Blodgett found that the cessation of emesis was hastened by giving small amounts of food at a time irrespective of the kind allowed. Howland and Marriott (Amer. Jour. of Dis. of Children, May, 1916) deem a 4 per cent. solution intravenously the method of choice, 75 to 150 c.c. (2½ to 5 ounces), according to the age of the infant, being given and repeated in three hours if the air-hunger does not cease.

The immediate administration of alkalies is warranted by the following group of symptoms: enlargement of the liver, hyperpnea, vomiting, thirst, dry mouth and lips, restlessness, acetone odor of the breath, strong odor of ammonia in the urine, and heavy acetone ring in the urine. Alkaline

treatment is advisable in all infant diarrheas, and the routine use of alkaline fever mixtures as a preventive. For most purposes a 4 per cent. solution in **glucose** or **cereal water** by mouth, or the same strength intravenously, is best. If there is no diarrhea they may be given by the bowel, and when there is vomiting small doses of a more concentrated solution may be given. A large draft of water should be taken 3 or 4 times a day. R. C. Connor (Interstate Med. Jour., Aug., 1918).

In the *acidosis of pregnancy*, H. Williamson (Amer. Med., June, 1916) says that chloroform anesthesia, calomel, and also mercurial douches should be avoided. Intravenous infusion with **sodium bicarbonate** or **sodium acetate** solution should be employed. **Glucose** should be administered so that the fat metabolism may be spared. If acidosis exists in a pregnant woman suffering from chronic nephritis, the uterine cavity should be emptied.

In *operative acidosis*, A. C. Burnham (Amer. Med., June, 1916), recommends as routine treatment: (1) Adequate nutrition by mouth, especially in the form of **carbohydrates**; (2) forced carbohydrate feeding in the form of **glucose solutions** by mouth—a teaspoonful of glucose to a glass of water. It may also be given by rectum, or subcutaneously, an ounce to a quart; (3) **bicarbonate of sodium solutions** given by mouth, rectum or subcutaneously; (4) saline solutions by **hypodermoclysis** during the operation; and (5), **morphine** for the relief of pain and to prevent the evil effects of excessive external stimuli.

Acidosis is probably responsible for certain cases of sudden coma after an operation, collapse suggesting embolism, and sudden death. The lesions accompanying acidosis involve the liver, brain cells, suprarenals and thyroid, but they are generally temporary disturbances. They subside during natural sleep, but not during repose without sleep. The ammonia content of the urine is an index of the resisting powers. With 2 Gm. in the urine the acidosis must be regarded as grave, but not irre-

mediable; with 3 Gm. the prognosis is bad. In normal conditions, 10 Gm.* (2½ drams) of sodium bicarbonate renders the urine alkaline, but in case of acidosis, 20, 40 or 50 Gm. (5, 10 or 12½ drams) are necessary. The main point, however, is to ward off the acidosis by diet, copious supply of fluids, stimulants, and keeping the patient quiet, tranquil and cheerful. F. Jeunet (Presse méd., May 13, 1918).

Acidosis in various disorders such as diabetes, shock, diarrhea, etc., are considered under their respective headings.

C. E. DE M. SAJOUS,
Philadelphia.

AUTOSEROTHERAPY. See

ASCITES, TREATMENT OF.

AVIATORS' SICKNESS designates the disturbances experienced by aviators owing to rapid changes of altitude which flying entails.

SYMPTOMS.—The symptom complex of this disorder has been clearly described by M. G. Ferry, medical officer of a French aviation camp after a large number of personal ascents in various types of airplanes (Presse médicale, January 6, 1916). He states that during ascent, the rapid or slow adaptation of the body—according to the speed—of the organism to the surrounding medium is attended by various physiological disorders varying with the altitude. These, often insignificant and transitory, have in great part escaped the notice of aviators. Headache frequently appears on reaching beyond an altitude of 1500 m. (Blériot monoplane), 2000 (Ferman biplane); tinnitus aurium at the same altitude—especially when the motor is placed behind the seat, or when it is not rotatory; increasing difficulty of inspiration—associated with augmented facility of expiration in the rarefied air; rapidity and tenuity of the pulse, according to the increase of altitude reached.

Those various unpleasant sensations seem to decrease slightly on assuming the horizontal plane at the highest altitude attained. When, however, any disturbing incidents occur, such as eddying currents, slight repetition of the respiratory or car-

diac troubles supervene—of emotional or reflex nature, which, however, soon subside.

The descent is attended by sensations more sharply defined in proportion to the velocity and the degree of agitation. The headache disappears—but at an altitude somewhat below that of its original onset. The respiratory movements return by degrees to their normal rhythm, the pulse becomes slower with a more vigorous stroke—although more gradually. Tinnitus aurium, however, subsides but slightly and persists even after reaching the ground for a period which varies with the form and location of the motor—3 to 4 hours when the motors are fixed at the back; ½ to 1 hour when the rotatory apparatus is placed in front of the aviator. An auriculo-tympanic shock is also produced by the act of deglutition during descent, which results from the brusque re-establishment of equality of pressure on the 2 faces of the tympanic membrane. The painful sensation of throbbing strokes which synchronise with the pulse cease while the hearing is improved. When the descent is carried out in short spirals with deep grades, the machine being sharply inclined, palpitation possibly of emotional origin, sometimes appears. Swooning of short duration may follow. A distinct nervous excitation also follows the landing, manifested in tremor of the extremities and muscular twitchings, slight incoordination of movements, brief periods of palpitation, local congestions of the face, an intense desire to urinate (often unjustified by bladder distention), and increased appetite. All these manifestations soon disappear and are replaced by fatigue and an imperative need of sleep. Some experience severe headache which is usually also relieved by deep sleep.

Combats between aviators generally occur at altitudes between 4000 and 5000 meters, with the barometer at 47 to 41. The temperature descends by 1° C. for every rise of 110 meters at the lower altitudes and for every 200 metres at high altitudes. During an ascent general lassitude may be experienced as a result of the reduction in atmospheric pressure. In full flight, at about 5000 meters,

the aviator may experience pain in the ears, heaviness of the head, somnolence, general fatigue, and apathy. During the descent there may be renewed pain in the ears and tinnitus. Upon alighting there may be temporary deafness and at times a staggering gait. Otoscopy then shows congestion of the entire auditory apparatus. The ear disturbances are due in particular to differences in atmospheric pressure. Hence the relief secured during ascent by Valsalva's method, and during descent, by that of Toynbee. A. Castex (Bull. de l'Acad. de Méd., June 25, 1918).

ETIOLOGY.—The disturbances are the result of the rarefied air, and are the same as those experienced by mountain climbers, owing to the low barometric pressure, according to Aggazzotti (Riforma Medica, Apr. 27, 1918). Acute pain in the normal ear is not a direct symptom from this cause, but is indirectly due to it. The conditions producing it are corrected by making swallowing movements, working the jaws, and yawning. There may be minute bleeding from the superficial vessels in lips and nasal mucosa, but the cold prevents extensive hemorrhage, and such has never been observed.

He accepts Mosso's explanation of the disturbances in rarefied air as due to changes in the gases of the blood, especially impoverishment of oxygen and of carbon dioxide. The proof of this assumption is provided by the absence of these disturbances, even in extremely rarefied air, if the blood is kept supplied with oxygen and carbon dioxide. In experiments at the Institute of Physiology at Turin, he was able to bear perfectly a barometric pressure of 140 mm.—which corresponds to an altitude of 13,491 meters—when he breathed a gas mixture consisting of 67 per cent. oxygen and 12.7 per cent. carbon dioxide. He used in this way 11 liters of the mixture, breathing naturally, without the slightest disturbance of any kind. With a mixture consisting of 67.8 per cent. oxygen and 13.4 per cent. carbon dioxide he found that all was well with him even at a barometric pressure of only 122 mm., corresponding to 14,589

meters. A higher altitude than this has never been reached in aeroplanes or in the pneumatic cabinet. His mind was clear, vision normal, his movements certain, with no tremor of the lips or sensation of heat in the face.

When aviators begin to feel disturbances from the rarefaction of the air, they should make muscular movements; this will improve the oxygenation of the blood, since respiration will become more active, and carbon dioxide will be produced in the muscles and pass into the blood.

PATHOLOGY.—In a large proportion of mysterious crashes to earth, the cause, according to Surgeon Panter (Jour. Royal Naval Med. Service, Jan., 1918), is loss of consciousness by the pilot. He has had at least 4 cases of pilots completely losing consciousness in the air. Two of these "crashed" on trying to land, which apparently they did subconsciously, without severe injury to themselves, the other 2 both lost consciousness at a height, subsequently regaining it, and were able to recover control of the machine and make safe landings, both feeling extremely ill. He has often noticed how greatly any alimentary disturbance becomes exaggerated in the air, and several cases of vomiting while flying have occurred apart from vestibular vomiting experienced by some pilots on extremely "bumpy" days. In these cases also the pilot, on questioning, has admitted having had slight indigestion before going up. A common cold when accompanied by much nasal catarrh will often give rise to great trouble at a height, and especially during rapid diving, and several times pilots with this condition have come for advice wishing to ascribe their symptoms to a "lack of oxygen," but with the curing of the cold the trouble ceases. For efficiency in the air, robust health is essential. Any minor disability becomes greatly accentuated when the general nervous system is at high tension, as during flight, and there is not the slightest doubt that many "crashes" and "nervous breakdowns" could be averted if all minor maladies were taken in time and brought under treatment.

The influence of flying on the blood was studied by Kaulen (Deut. med. Woch., Dec. 13, 1917). He found that aviation

produces an increase of red blood-corpuscles and of the percentage of hæmoglobin. This is distinctly noticeable after 3 months of aviation and is not due to a concentration of the blood from greater viscosity. The leucocytes do not follow a parallel increase. The phenomenon does not occur during a single ascension. This multiplication of the red blood cells is not accompanied by the appearance of nucleated cells, but polychromatophiles may appear. The blood of rabbits and mice carried in the aeroplanes was found to offer similar changes to those met with in man.

PROPHYLAXIS.—The prevention or at least mitigation of the disorders incident upon aviation is closely associated with the absence of all physical defects in the aviator. As urged by J. C. McWalter (*Med. Press*, Aug. 21, 1918), of the British Medical Flying Board, whose observations accurately summarize those of other medical officers, the physical qualifications of a flying officer become higher every day. Men who can fly with ease at 5000 or 6000 feet may be useless for some modern conditions of warfare where machines are worthless unless they can fly at 15,000 to 20,000 feet or more. Troubles due to extreme cold, or to atmospheric rarefaction at great heights, may be minimized by the use of oxygen and of warm clothing, but a marvellously elastic vascular mechanism is required before a man can descend with impunity, and in a few minutes, from a height of 20,000 feet. The cardiac muscle must also be in a very healthy state in order to respond promptly to the strain on the circulation. The lungs and bronchial membranes must be not only sound, but proof against the irritation engendered by the heat and smoke of the engine or by the varying moisture of the air. All this means that a man must be young, athletic, fit, sound and strong.

A flying man may have all these qualifications and yet be defective. In actual practice, the author found that of men who have been passed as fit into the Flying Corps, whether by special medical boards or by ordinary medical officers, that gross lesions of the heart, lungs or abdominal organs are seldom present, but that notable defects often exist in the

nervous system, or in the ear or nose, less often in the eyes or throat.

The most usual—but the most dangerous, defect is some disease of the labyrinth. This is often overlooked, being unlikely, in its milder forms, to cause any acute trouble until the patient has mounted some thousands of feet; it then gives rise not only to vertigo and giddiness, but to a lack of that sense of equilibration and location which is of the essence of the successful flying man. One has also found that those flying men who experience most difficulty in judging of the distance of the ground when approaching a landing place, are frequently the subjects of this disorder.

The whole series of rhinological ailments, stenosis, sinusitis, hypertrophy of the turbinated bones, Eustachian tube troubles, even pharyngitis and tonsillitis—all render, in greater or less degree, a man unfit to fly.

Emphasizing the importance of cardiovascular disturbances as a cause of aviation accidents, the writer states that high altitudes may induce unconsciousness through additional diminution of blood-pressure in subjects already suffering from low tension, due to cardiovascular disease. The aviator with initially low pressure is likewise threatened with syncope when the pressure drops too rapidly, and this probably accounts for the sudden falls to death of numerous aviators. The blood-pressure of all aviators should be tested periodically, with special examination of those who report nervous disturbances, dyspnea while in flight, or who have hepatic trouble. An aviator with a diastolic pressure of 60 (Pachon) or below should be considered temporarily disqualified for the work. D. Berthier (*Bull. de l'Acad. de méd.*, Sept. 10, 1918).

The importance of perfect vision has been emphasized by Naval Surgeon H. G. Anderson (*Lancet*, Mar. 16, 1918). He holds that the aviator should have unaided normal vision in each eye separately, and normal color perception. In the writer's experience, which includes much actual flying, the vision had more to do

with determination of position in space than any other sense. Those with defective vision are at a great *disadvantage* in an aerial flight on making landing. The presence of heterophoria, or latent squint, has also been found a cause for making bad landings. Concealed hypermetropia should cause rejection if sufficient to enable a candidate to read 6/9 each eye, with a plus 2 lens. *The importance of perfect color perception is very great.* Its use comes in picking out the color or markings of hostile machines, in recognizing signal lights, and in judging the nature of landing grounds. Night blindness is important in selecting pilots for night bombing. Night blindness is tested by reading ordinary test cards under increased or decreased illumination.

A curious feature to which the same writer calls attention is the fact that it has been found in a fog that it is almost impossible to detect any deviations of position during a flight. Aviators have come out of dark clouds or fogs and found themselves flying one wing down, or even upside down, without knowing it. Therefore most of the impressions which control balance in flying come from the eyes. He advises a thorough investigation into the candidate's equilibrium, muscle sense, and vestibular reaction. In addition to those tests, the psychomotive reactions should be thoroughly gone into, and the aviator should possess a normal reaction time with regard to vision, hearing, and touch.

Results of over 1000 observations in the aviation tests for equilibration by means of the Bárány chair (see article on INTERNAL EAR, in the fourth volume), and a collaborative determination of the corresponding pulse rate. Taking the general average it can be said that in 100 cases the stimulation to the vestibular portion of the eighth cranial nerve end-organ by 50 revolutions, at varying rates of speed, produced an increase in the rate of heart action of 9 beats per minute. Babcock (Boston Med. and Surg. Jour., Dec. 13, 1917).

Recently, in Italy, Colonel Gradenigo stated that he considered it was sufficient to test only for nystagmus

and not for pastpointing and falling, because a normal nystagmus alone showed that the internal ears were normal. The reason the other tests were made in America, however, was due to the realization that it was not an end organ alone that was being dealt with, but with a test of a large portion of the central nervous system, most particularly the cerebellum. It had been observed by many fliers that one instructor flew in a peculiar way; he would allow either one wing or the other to be tilted to a dangerous degree without making any effort to correct it. This was true when he was at a high altitude and also at a low altitude; but on nearing the ground, when he could orient himself by the sense of sight, he would straighten out and land satisfactorily. On one occasion he was flying over Philadelphia and entered a cloud; his passenger was an experienced aviator who became alarmed at the manner in which the plane was being guided. This passenger could detect deviations in position which apparently meant nothing to the pilot and which resulted in a dangerous sideslip. Examination in the turning chair on the following day showed that the pilot had practically no responses in nystagmus, vertigo, pastpointing, and falling whereas the passenger showed entirely normal responses. I. H. Jones (Trans. N. Y. Neurol. Soc.; N. Y. Med. Jour., Jan. 11, 1919).

Finally, as emphasized by Bernard (Progrès Médical, May 11, 1918), aviators should constantly be objects of study, the task of the physician being almost exclusively towards lines of prophylaxis. Even when aviators are fitted for the service, surveillance should be incessant. He should live among them, watch the physical and moral modifications induced by flying, study each accident minutely to learn how such can be avoided. The training camp should have a commission for study of these problems, including a physiologist, a physician, a surgeon, an ophthalmologist, a neurologist and an ear, nose and throat specialist. S.

BACTERIAL VACCINES.—

Bacterial vaccines are preparations of bacteria, or of their products, for prophylactic or therapeutic use. In the usual liquid form the vaccines are clear, slightly opalescent, or milky, the appearance depending upon the amount of bacterial substance in them. There may be sedimentation. A small percentage of an antiseptic (phenol, tricresol, or liquor cresolis comp.) is added to fluid preparations as a preservative. The vaccine usually contains the whole bacterial cell treated by exposure to a temperature just sufficient to destroy its reproductive function. Heat, however, is not always applied, the preservative being sometimes relied upon for sterilization. In lieu of heat other substances have been recommended, *e.g.*, galactose.

Sometimes living attenuated bacteria are employed; again, extremely small amounts of highly virulent germs are injected, while still another class of vaccinating substances consists of bacterial products. These include bacteria split mechanically, chemically, or by autolysis, and bacterial toxins or filtrates of fluid cultures. Besredka has suggested so-called sensitized vaccines, *i.e.*, bacteria treated with their homologous specific immune sera.

Bacterial vaccines are used both to prevent and to cure infectious diseases. They are believed to accomplish this by stimulating the healthy tissues to produce substances which reinforce the normal anti-infectious powers of the body. When brought into direct contact with healthy tissues, the vaccine causes the normal cells to exercise their ability to remove foreign proteins. To accomplish this they manufacture in great abundance specific substances antagonistic to the bacteria, called antibodies. These find their way into the

circulating blood and aid the cells engaged in actual combat with the bacteria at the focus of infection. In the prophylactic use of vaccines the antibodies are stored in the blood and tissue juices ready to meet invading bacteria. The sole effect of the vaccine is the generation of antibodies and the sole action of the antibodies is upon the bacteria; therefore, it is obvious that the ultimate purpose of the vaccine will fail unless the antibodies in the blood are able to come into direct contact with the bacteria. The pathological conditions about the focus of infection are often such that accessory methods of treatment are necessary to accomplish this end. Vaccine inoculation does not preclude the ordinary methods of treatment.

Bacterial vaccines are usually administered by subcutaneous injection, though they may be given intramuscularly or even intracutaneously; there seems to be no sufficient reason for intravenous administration. They have been given by the mouth and, with certain restrictions, the results have apparently been satisfactory.

HISTORY.—Bacterial vaccine therapy is the direct outcome of studies in immunity. Immunity is resistance to disease. Until very recently the methods practised to limit and control infectious diseases were held to be empirical, and progress seemed to be the result of accident rather than of systematic investigation; but when we thoroughly examine the history of therapeutic inoculation, we come upon illuminating facts that are not flattering to our pride in modern achievement.

While history does not reveal the precise origin and development of the methods first practised, certain isolated evidences lead us to believe that in

medicine, as in other sciences, much valuable knowledge has been lost to us. According to Pliny, Mithridates Eupator, in the first century B. C., so accustomed himself to all known poisons that none could harm him. Behring believes that knowledge of such possibilities is responsible for the Hippocratic dogma that the same factor that produces the disease is also capable of preventing it—the fundamental principle of modern homeopathy.

Descriptions by travelers of methods used by savages to protect themselves from the effects of arrow-poisons and snake-venoms are truly remarkable. Such stories suggest that these procedures are, as it were, the remnants of greater knowledge preserved among an unprogressive people. Possibly their teachers, with ever-changing modes, moved on to other scientific fashions and neglected valuable and practical facts. In this connection, Metchnikoff (*L'Immunité dans les Maladies Infectieuses*, Metchnikoff, Paris, Masson, 1901) gives the instance of Serpa-Pinto, who was immunized to snake-venom by the Vatuas, natives of the east coast of Africa. In this tribe it is the custom to extract the poison from venomous reptiles and mix it with certain herbs into a paste, which is then applied to incisions made in the skin—a painful operation followed by a swelling lasting a week. The Vatuas declare that this procedure confers a certain immunity to snake-bite. Subsequent occurrences appear to prove that Serpa-Pinto was actually immunized by this treatment. The Senegambians are said to have a method of vaccinating their cattle against bovine peripneumonia; it is certain that such a method has been known in Europe for more than a century. Inoculation against small-pox

appears to have been used in Asia for hundreds of years. The Chinese claim to have employed a method of inoculation, upon the septum of the nose, since the beginning of the eleventh century. Some writers believe that such procedures originated with the Arabian physicians, and that the practice was carried by Tartar and Chinese traders to Bengal and China.

The first publication in England describing inoculation was written by Kennedy in 1715. He stated that those who practised it asserted that it was no worse than taking the itch. The relative harmlessness claimed for inoculation did not attract serious attention until Lady Mary Wortley Montagu persuaded the profession in England to take it up. In 1721 the method was openly employed, and the success reported caused it to be used in other countries of Europe. It was brought to America during the epidemic of 1721. It is needless to say that, even though practised upon persons in good health, and the material taken from persons with only a mild attack of the disease, the inoculation was not without danger. In England the practice continued until 1840.

In certain districts of England a belief had long existed among the dairy-folk that a disease of cattle known as cow-pox, when communicated to the milkers, protected them against small-pox. It seems likely that this fact was noted particularly on account of the resistance to inoculation with small-pox of persons who had had cow-pox. Although there was apparently considerable general interest aroused by this circumstance, Edward Jenner is popularly held to have first recognized its possibilities.

[According to Alexander von Humboldt, vaccination with cow-pox had been practised by Indian shepherds of the Mexican Cordilleras "since the earliest recollection of man." Brun speaks in much the same way in reference to the Elihats of Beluchistan. The belief was general that accidental inoculation of cow-pox by the dairy-folk of England, existing prior to Jenner, in at least eighteen counties, rendered the milkers immune to small-pox.

It was a dairymaid, as is well known, who brought the fact to the notice of

his first report to the Royal Society in 1796 or early in 1797. It was rejected and in 1798 was published independently. The beneficial results of cow-pox inoculation were demonstrated almost immediately. The number of deaths from small-pox in London decreased from 17,867 and 18,477, in the last two decades of the eighteenth century, to 12,534 and 7856 in the first two decades of the nineteenth century.

SMALL-POX DEATHS.

Population.		1886	1887	1888	1889	Average of deaths.	Average per million of population.	
Compulsory vaccination.	Sweden	4,746,465	1	5	9	2	4	1.0
	Ireland	4,808,728	2	14	3	0	5	1.0
	Scotland	4,013,029	24	17	0	6	12	3.0
	Germany	47,923,735	197	168	112	200	169	3.5
	England	28,247,151	275	505	1,026	23	458	16.0
	Switzerland	2,922,430	182	14	17	3	54	18.5
	Belgium	5,940,365	1,213	610	865	1,212	975	164.0
	Russia	92,822,470	16,938	25,884	*	*	21,411	231.0
	Austria	23,000,000	8,794	9,591	14,138	12,358	11,220	510.0
	Italy	29,717,982	*	16,249	18,110	13,416	15,925	536.0
Spain	11,864,000	*	*	14,378	8,472	11,425	963.0	

*No statistics available.

Jenner. The first intentional inoculation was made by Benjamin Jesty, of Dorsetshire, in 1774. Small-pox was prevalent, and, though by accidental cow-pox inoculation Jesty was himself immune, he inoculated his wife and two sons near the elbow from the teats of the cows. Fifteen years later, i.e., in 1789, the sons were inoculated by Mr. Trowbridge, for small-pox, together with others who had not been inoculated with cow-pox. The two Jesty boys escaped, but the unprotected went through the usual course of inoculated small-pox. Subsequent exposure to small-pox by Mrs. Jesty and the sons demonstrated their immunity. Twenty-two years after the vaccination of the Jesty family, Jenner vaccinated the Phipps boy.]

After giving this subject careful study for many years, Jenner presented

The above table from Welch and Schamberg ("Acute Contagious Diseases," Phila., Lea, 1905, p. 126) shows the incidence of small-pox where vaccination is compulsory compared with its occurrence in those countries where it is not compulsory.

Nearly a century elapsed before further progress was made in artificial immunization. So long as the actual agents causing the disease remained undiscovered, empirical progress alone was possible. But with improvements in optical instruments the microscopic forms of life were discovered and the relation of micro-organisms to disease, long before suspected, was actually demonstrated. *Anthrax* was the sub-

ject of this first demonstration. In 1850 Davaine observed and described anthrax bacilli in the blood of infected animals, and in 1863, finding that they were constantly present, he suggested that they were the cause of the disease. In 1860 Delaford had cultivated them artificially in blood, and in 1876 Koch grew the anthrax bacilli on a solid medium. This work was confirmed and continued by Pasteur; both he and Koch reproduced the disease in animals.

Pasteur familiarized himself thoroughly with the prevention of small-pox by vaccination, hoping that other communicable diseases might be combated in a similar manner. Chance seems to have favored him. He had been working with his collaborators, Roux and Chamberland, upon chicken-cholera. A bacillus had been isolated the pure cultures of which could be kept alive in broth. When inoculated with these broth-cultures, healthy chickens never having had cholera, died with the typical symptoms. Identical bacilli were obtainable from the dead chickens. Upon their return from a vacation in the fall of 1879 the work was again taken up. Much to the surprise of Pasteur the broth-cultures, which had been stored away, failed to kill chickens even though the injections were in quantities much larger than in the former experiments. He immediately obtained fresh cultures from chickens which had contracted the disease spontaneously, and again demonstrated their virulence and deadly effect on normal fowls. The chickens which had been inoculated with the old cultures now proved to be entirely refractory even to large doses of highly virulent bacilli. Pasteur, whose mind

had been dwelling constantly upon the problem of the prevention of disease, immediately recognized the two facts which are the foundation of vaccine prophylaxis and vaccine therapy, namely, that *bacteria may be attenuated*, and that *attenuated bacteria may be used for vaccination*.

Believing the refractory state of the chickens to be identical with that of man after cow-pox inoculation, Pasteur called the process "vaccination." Thus, although the word "vaccine" is derived from "*vacca*," and primarily refers to the bovine species, there is sufficient justification for its retention to designate substances producing active immunity. Its use is also defensible in that it has been since 1880 the exclusive term in a literature already sufficiently burdened with newly coined words.

The work with chicken-cholera was duplicated in the case of anthrax and investigations on rabies were started.

Because of the extreme care with which every point was proved, and even after the successful immunization of dogs with attenuated spinal cord, it was five years before the first person was inoculated. Prophylactic vaccines were rapidly developed for various epizootics, such as rauschbrand, hog-erysipelas, etc. In epidemic diseases affecting man progress was necessarily slower because experimental work must proceed with greater caution. It was believed that immunity could be acquired only by recovery from a mild attack of the disease. Few were willing to submit to such a severe measure, especially when the incidence of the disease in question was not very high. It was, therefore, not until typhoid fever and bubonic plague necessitated extreme efforts and measures that Pasteur's

discoveries were extensively utilized. They would probably have remained unique instances if Wright had not elaborated methods whereby the mechanism of the changes following an inoculation could be closely observed.

By their discovery that animals could be immunized by the *products of bacteria*, Salmon and Smith opened a new field of research. Contrary to the popular belief at that time, they proved that it was not necessary to recover from an attack of a disease to become immune to it. The study of substances in the culture fluids and their relation to antagonistic properties of the blood of treated animals inaugurated work along what may be considered chemical lines instead of the previously purely biological ones. So early as 1874, Traube and Gscheiden found that normal blood had bactericidal properties, and in 1887 Buchner, and later Nuttall, confirmed this and investigated it in detail. Discoveries of the highest importance appearing in rapid succession were the outcome of studies concerning the effect of culture fluids upon animals, and the protective power of the blood-serum of these animals. In 1888 Roux and Yersin discovered diphtheria toxin; in 1890 Behring announced the discovery of diphtheria antitoxin, and, shortly after, in collaboration with Kitasato, he prepared tetanus antitoxin. To Behring is due the credit of establishing the law that *the serum of an artificially immunized animal may transmit immunity to other animals* (passive immunity). At this point practical developments in the preparation of antitoxins ceased, because tetanus and diphtheria (and botulismus) are the only diseases due solely to the action of soluble bacterial poisons. Progress continued, however,

in the development of our knowledge of the reactions on the part of the tissues following the inoculation of foreign proteins. In 1891 Ehrlich demonstrated the development of substances antagonistic to the toxic effect of abrin and ricin in the blood of animals treated by the injection of gradually increasing doses of these vegetable poisons. He studied the relations between these poisons and the antibodies in the blood-serum and learned the mechanism of *toxin neutralization*, elaborating from this the present method of standardizing diphtheria antitoxin.

In 1894 Calmette prepared serums with neutralizing properties for snake-venoms. In the same year, by injecting the washed erythrocytes of one animal into an animal of another species, Bordet produced in the second animal substances with the power of dissolving the red corpuscles of the first. These are called *hemolytic* serums. Another variety of the same class, *cytolytic* serums, have the power of dissolving or destroying tissue cells. In all cases the animal furnishing the cells and the animal injected must be of different species. *Bacteriolytic* power is one of the acquired properties of the serum of animals injected with bacteria.

According to Nicolle the work on *anaphylaxis* has shown that not only body cells and bacterial cells (*i.e.*, formed elements), when injected into an animal, undergo digestion, with the resultant formation of an excess of digestive or lytic substances, but that also unformed substances or proteins undergo the same process. In other words, the protein molecule is split into simpler substances so that it may be absorbed and eliminated. Further study has proved that several classes of sub-

stances, with different functions, are developed in the blood of animals treated with organized and unorganized protein substances. These antagonistic substances are called *antibodies* and,

are the direct outcome of work along definite lines, most of it planned to demonstrate the soundness of certain theories devised to explain the occurrence of phenomena already known.

LIST OF IMMUNIZING BODIES AND THEIR ANTIBODIES.

Antigens or immunizing substances.	Products of immunization.	
Toxins.	Antitoxins.	
Complements.	Anticomplements.	
Ferments.	Antiferments.	
Precipitogenous substances.	Precipitins.	
Agglutinogenous substances.	Agglutinins.	
Opsonigenous substances of bacteria.	Opsonins.	
Cytotoxin-producing substances.	Cytotoxins.	<div style="display: inline-block; vertical-align: middle;"> <div style="font-size: 3em; vertical-align: middle; margin-right: 5px;">{</div> <div> Hemolysins. Bacteriolysins. Special cytotoxins. Spermatotoxin. Nephrotoxin. Hepatotoxin. Neurotoxin. Syncytiolysin, etc. </div> </div>
		Consisting of two bodies, <i>i.e.</i> , complement and amboceptor.

IMMUNIZATION WITH ANTIBODIES.

Precipitins.	Antiprecipitins.	<div style="display: inline-block; vertical-align: middle;"> <div style="font-size: 3em; vertical-align: middle; margin-right: 5px;">{</div> <div> Consisting either of anticomplements or antiamboceptors; the latter may be an antibody for the complementophilous or for the cytophilous haptophore of the amboceptor. </div> </div>
Agglutinins.	Antiagglutinins (?).	
Cytotoxins.	Anticytotoxins.	
Hemolysins, etc.	Antihemolysins, etc.	

SYNONYMS.

Complement.	Amboceptor.
Alexin.	Immunkörper.
Cytase.	Zwischenkörper.
	Intermediary body.
	Substance sensibilicatrice.
	Fixator.
	Preparator.
	Copula.
	Desmon.

(From Ricketts and Dick, "Infection, Immunity, and Serum Therapy," Chicago, Amer. Med. Assn. Press, 1911, p. 361.)

the proteins used to generate them, *antigens*.

THEORIES OF IMMUNITY.—

Few of these discoveries and developments in our knowledge of immunity have been the result of chance. They

The first of these theories—that of Pasteur—is based upon his observation that the chicken-cholera bacillus could not be grown in the filtrate from a well-developed bouillon culture of the same organism. He says: "The muscle

which has been the seat of severe disease has become, even after recovery and healing, in some manner unable to support this microbe, as if this latter, by a previous growth, had exhausted in the muscle some principle which is not restored and the absence of which inhibits the development of the organism." He believed that the mechanism of acquired immunity depended upon the exhaustion of certain elements necessary for the development of the bacterium in question.

This theory, recently revived by Ehrlich under the name "athrepsia" to account for the spontaneous retrogression of certain cancers, appeared very plausible. Among those interested was Chauveau, who, although believing there was considerable experimental evidence to support Pasteur's hypothesis, thought that some observations of his own showed it to be untenable. Chauveau found that he could with impunity inoculate Algerian sheep with virulent anthrax bacilli in amounts certainly fatal for ordinary sheep, but if the dose given was very large a fatal attack of anthrax developed. He believed such results proved that immunity depended therefore not on an exhaustion of something essential to the growth of the bacteria, but upon something added to the body fluids.

The most striking point about these two hypotheses is that they both consider the body entirely passive in its resistance to infectious disease. One theory supposed that the bacteria take some property away from the body; the other, that they add some property to it.

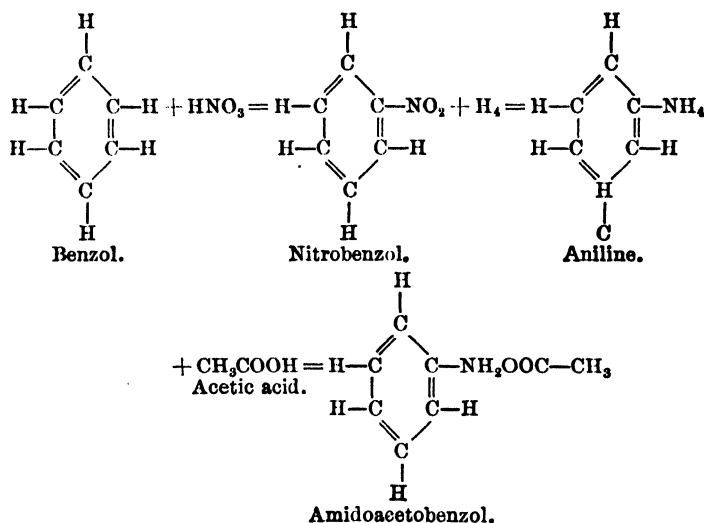
The Phagocytic Theory of Metchnikoff.—The activity of the white corpuscles of the blood toward foreign

particles had been noted by Virchow in 1840, and attention had been directed to their behavior toward bacteria by Koch in 1878. The first supposition that they might have some relation to immunity was made by Karl Roser in 1881. Sternberg also suggested that phagocytosis might in some way be related to immunity. Little attention was given the subject until 1884, when Metchnikoff published the results of his observations upon the activity of the leucocytes in the water-flea. The water-flea, or daphnia, is a minute aquatic animal the body of which is transparent. It is subject to a disease caused by a blastomyces. Metchnikoff observed that after the spores of this fungus had been swallowed by the animal they penetrated the intestinal wall and, entering the body cavity, were surrounded by leucocytes. The leucocytes ingested the spores and frequently caused their entire disappearance, in which case the disease was overcome. Sometimes, however, the spores were not destroyed, but developed and apparently acquired the power of killing the animal with blastomycosis.

With this observation as the starting point, Metchnikoff studied the white corpuscles of man and their relation to bacteria. He thus arrived at the promulgation of the phagocytic theory of immunity. White blood-corpuscles in the act of ingesting bacteria he called "phagocytes." The phagocytic theory of Metchnikoff supposes that immunity to infectious disease depends upon the phagocytosis of the bacteria and their destruction by a digestive process which goes on within the leucocyte. Artificial immunization increases the phagocytic power and in this way acquired immunity is established.

The Theory of Ehrlich.—In 1885, Ehrlich, in Germany, published a little work on the oxygen requirements of the body, in which he expressed the belief that the assimilation of foods by the body cells is accomplished by a chemical union between the food substances and some constituent of the cell. It was not his understanding that assimilation is accomplished merely by this union, because certain molecules of

fourth bond of each carbon atom is linked to an atom of hydrogen. It is well known that one or more of the atoms of hydrogen may be replaced by a great variety of radicals, and by substituting such radicals an infinite number of chemical compounds may be produced. The groups which have been substituted are called "side chains." Thus, by substituting various side chains in succession we arrive at the



complex composition must be split into simpler substances before they can become a part of the protoplasm. For this reason the cell constituent which combines with the nutritious molecule serves only as a link to bring the food-stuff into relation with the digestive, oxygenizing, or fermenting activities of the cell. Ehrlich believes that his theory may be more easily understood if we liken the center of activity of the cell to the benzol ring. The molecule of benzol is C_6H_6 . In the graphic representation of this formula each carbon atom is linked to two other carbon atoms in such a way that each one has three bonds of affinity satisfied. The

compound known commonly as acetanilid.

In exactly the same way the body cells have bonds of affinity capable of combining with various substances which are to be utilized by the cell for its nourishment.

Ehrlich further believes that the side chains of a cell consist of definite groups of atoms capable of uniting chemically with certain other definite groups of atoms in the food particles. The side chains of the cells are called *receptors*, while the combining groups of atoms of the food substances Ehrlich calls *haptophore groups*. Now, as we know, different foods have different chemical

compositions, and Ehrlich believes it likely that the binding groups or receptors of the cells are also different in chemical composition and affinity to agree with the peculiar affinities of the food materials. In other words, it is a fundamental requirement of this theory that there must be as many different kinds of receptors as there are substances capable of uniting with the cell.

In order to explain the formation of antibodies by the side-chain theory of nutrition Ehrlich supposes that all protein materials, not only those used for the nourishment of the cells, but also toxins and other substances harmful to the cell, unite with the receptors in the same way. Instead, however, of the receptor acting merely as a link between the food material and the cell, in the case of noxious substances, an effort is made to protect the cell by eliminating the affected receptor. When the receptor has been eliminated a wound or defect is left upon the cell. This wound is healed by the production of new receptors, and, as occurs in all reparative processes, an excess of material is manufactured. But as only one receptor is necessary to replace it all others are thrown off into the body fluids. Blood-serum rich in such receptors constitutes the immune serum resulting from the treatment of an animal with specific proteins. In other words, the free receptors in the blood-serum are the immune bodies.

The cells of the body may possess no receptors for certain protein substances, and when this is the case the animal is naturally immune to these substances; for example, the human body has no receptors for the substances which cause hog-cholera.

There are, as it has been said, as

many different receptors as there are substances which can unite with the cell. There are likewise several classes of receptors with regard to their relation to and effect upon the antigen. By *antigen* we understand the substance used to stimulate the production of receptors, or, as they are collectively called, antibodies. After these have been set free by the cell they become a constituent of the serum and may be handled as such. They may be recognized and their quantity estimated by test-tube experiments just as if they were chemical substances. To Behring we owe the discovery that in the blood-serum, or a derivative of it, antibodies may be transferred to another animal with specific effect either in the treatment or in the prevention of the disease in question.

The theories of Metchnikoff and Ehrlich seeking to explain the various phenomena of resistance to and recovery from infectious disease, while possessing little in common, are not essentially contradictory. Each theory is based upon the ordinary processes of the body, that is to say, those concerned directly with the nutrition of the body cells. Metchnikoff held at first that the leucocytes, and they alone, were the agents responsible for meeting in combat the bacteria invading the body tissues, and that the issue of this combat is either immunity or an infection which may result in recovery, chronicity, or death.

Ehrlich and his school worked along chemical lines, and while recognizing the phenomenon of phagocytosis did not attach great importance to it. According to this school, acquired immunity is the result of phenomena which may be explained upon chemical

grounds, and that practically all the changes taking place in the tissues may be demonstrated in the test-tube. With the serum of an immune animal, for instance, toxins may be neutralized and bacteria killed and digested. As first shown by Bordet, two substances are necessary to accomplish the destruction of micro-organisms; one is the newly formed substance appearing in the blood-serum as a result of immunization; the other (called complement, because it completes the action of the first) is present in any fresh serum whether the animal has been immunized or not. The complement is thermolabile, that is, a moderate degree of heat will destroy it, and it cannot be preserved for more than a very few days.

The Theory of Metchnikoff.—Metchnikoff holds that the complement is derived from the leucocytes and also that it is not set free until the leucocytes are destroyed. Briefly, there is no free complement in the circulating blood under ordinary circumstances.

This was Metchnikoff's most important point after the school of Ehrlich had demonstrated that practically all the reactions of immunity could take place outside the body without the leucocytes. This final point was shown by Wright to be the neutral ground between the two theories of Ehrlich and Metchnikoff. Wright demonstrated that leucocytes are necessary to the body in overcoming or resisting the effects of bacteria, while the body fluids are equally important in that they prepare the bacteria for final ingestion and digestion. When it was demonstrated that there is more phagocytosis in a mixture of leucocytes, immune serum, and streptococci, than in a mixture of normal serum, leucocytes, and strepto-

cocci, Metchnikoff believed that this proved the presence in the serum of a substance stimulating the leucocytes to greater activity. He called this substance *stimulin*.

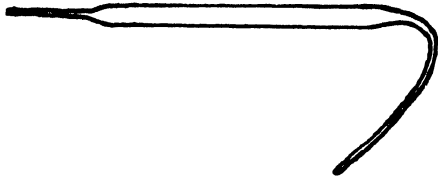
Denys and Leclef were the first to question the exact function of the so-called stimulin. Their work led them to believe that the immune body in the serum of a treated animal does not essentially affect the leucocytes, but that its chief effect is upon the bacteria, changing them in some way so that they are more easily ingested by the leucocytes.

Having in mind the observation of Metchnikoff and others with regard to increased phagocytosis in a mixture containing immune serum, Leishman attempted to determine whether he could estimate the degree of immunity of a vaccinated person by observing the relative amount of phagocytosis in mixtures containing normal serum compared with one containing serum from immunized persons. For this purpose Leishman measured in a capillary tube equal volumes of a bacterial suspension of appropriate density and blood drawn from the finger. These were mixed on a slide, covered with a cover-glass, and incubated at body temperature for fifteen minutes. The slide and cover-glass were then drawn apart by a sliding movement, and the films thus obtained stained by Leishmann's modification (British Med. Jour., 1901) of Romanowski's stain and examined under the microscope. He estimated the average number of bacteria, per polymorphonuclear leucocyte, and compared it with a similar average calculated from specimens prepared with normal blood.

By this technique Leishmann was able

to show a certain relation between the degree of immunity of an inoculated person and the degree of phagocytosis. But since he did not take into consideration the work of Denys and Leclef, and believed that he was working with immune bodies which stimulated the leucocytes, his conclusions lost much of their significance.

Wright and Douglas ("Proceedings Royal Society," vol. lxxii, 1903) modified this technique by using capillary tubes instead of a slide and cover-glass for the incubation, afterward making film preparations in the ordinary way.



Wright capsule.

Furthermore, the coagulation of the blood was prevented by the use of sodium citrate, thus avoiding complications dependent upon coagulation, and making it possible to separate the white corpuscles from the blood-plasma by centrifugalizing, decanting, and washing. The first method elaborated by Wright and Douglas was further refined and modified to the opsonic-index technique with which we are at present familiar.

Technique of the Opsonic Index.—

Material Required:—

1. Incubator.
2. Sterilized solution of sodium citrate, 1.5 per cent.
3. Solution of sodium chloride, 1 per cent.
4. Two sedimentation tubes, small centrifuge tubes.
5. Wright's blood-capsules.

6. Pipettes, and rubber teat.
7. Microscope slides.
8. Bunsen burner with pilot light.
9. Emery paper.
10. Paraffin pencil.
11. Microscope with $\frac{1}{12}$ oil-immersion lens and No. 4 eye-piece.

Biological Requisites:—

1. Healthy blood-corpuscles washed free from serum.
2. An emulsion of bacteria in pure culture.
3. Serum of a healthy person (preferably the mixed serums from at least three healthy persons).
4. Serum of the infected person.

The object is to compare the average number of bacteria ingested by healthy leucocytes when incubated respectively with serums from healthy and from infected individuals.

Method of Obtaining and Preparing the Serum.—A bandage is wrapped tightly around the finger, starting at the proximal end. The finger is flexed and is pricked near the root of the nail with a sharp, sterile, glass needle. As the blood flows out it is collected in a Wright capsule. This is made by drawing out to capillary size, after softening them in the flame of a Bunsen burner or blowpipe, both ends of a glass tube about 4 mm. in diameter. The capsule between the capillary ends is about two inches long; one of the ends is recurved upon itself, describing about half a circle one inch in diameter. The curve will enhance the flow of blood by its siphon action. It is well to collect a sufficient quantity of blood, although the actual amount required is only about 0.1 c.c. When the blood has been collected, the capsule is sealed by passing it through the pilot light, care being taken not to heat the blood,

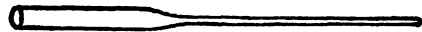
as heat will completely destroy the value of the serum. To hasten coagulation the capsule is incubated at 37° C., and in about twenty minutes the clot will have contracted sufficiently to allow the serum to be easily withdrawn without taking up any corpuscles. If necessary, the separation of the clot may be hastened by centrifugalization.

Preparation of the Blood-corpuscles.—A sedimentation tube is filled with sodium citrate solution to within one-half inch of the top. The blood from the finger obtained as described is collected by allowing it to drop into the sedimentation tube until this is nearly full,—8 or 10 drops. The tube is now closed with the finger and inverted several times to mix the blood and citrate solution. It is now centrifugalized to throw the blood-corpuscles to the bottom of the tube. The serum is in the supernatant fluid. The centrifugalization should not be continued longer than absolutely necessary. The supernatant fluid is withdrawn by means of a pipette, and a 1 per cent. salt solution is added to the corpuscles. After thoroughly mixing this, it is again centrifugalized. When the blood-corpuscles have been washed three times they are considered free from serum and are ready for use. Finally, the red and white corpuscles are intimately mixed.

Emulsion.—A good twenty-four-hour growth of bacteria on agar is advisable. A few drops of the salt solution are poured into a watch-glass, and a loopful of the culture is mixed with it. The suspension is made as even as possible by sucking the mixture into the pipette and then forcing it out. If any visible clumps remain, this suspension may be collected in the pipette, the end sealed,

the whole centrifugalized, and the supernatant fluid used. The suspension required is a very weak one, and it may even then be necessary to dilute the same with more salt solution. Most suspensions should be slightly opalescent.

The Opsonic Mixture.—A clean pipette is marked about three-fourths inch from its extremity with a paraffin pencil. It is necessary to take up equal volumes of corpuscles, emulsion, and serum, in the order named, in the one tube. All the material required should be conveniently arranged. The bottom of a Petri dish containing "plasticine"



Wright pipette.

makes the best holder for the tubes containing the materials. The tip of the pipette is dipped into the corpuscle suspension and the corpuscles are aspirated exactly to the mark. A slight bubble of air is next allowed to enter. The tip of the pipette is wiped and dipped into the bacterial emulsion. An equal amount of this is drawn up, another bubble of air is allowed to enter, and then by a similar procedure an equal volume of serum is added. These are now forced out upon a clean microscope slide by gentle pressure of the rubber teat. The mixture is then drawn back into the pipette as an unbroken column. This is aspirated in and out five or six times, and thereby mixed thoroughly. The tip of the pipette is then sealed in the pilot light of the Bunsen burner and the mixture is incubated at 37° C. for a suitable time (generally fifteen minutes), depending upon the kind of bacteria.

A control mixture is prepared in the same manner, containing the same cor-

puscles, the same bacterial emulsion, the serum being that of a healthy person (it is better to use the pooled serums from several healthy persons or to make several controls). This is incubated for the same length of time.

Preparation of the Opsonic Film.—After suitable incubation the pipettes are removed and one drop of the mixture is placed about one-half inch from the end of the slide, and is spread as smoothly as possible with a second slide or with a special, slightly concave spreader. In a well-spread film the white corpuscles will be found near the end of the smear. The film should end near the middle of the slide. A similar smear from the control pipette must also be made. The importance of a well-spread, smooth, thin film cannot be overestimated. The films are fixed by any of the ordinary methods, one of the most convenient being to place the slide, film downward, over a wide-mouth vessel containing 40 per cent. formalin. It is then stained with carbol-thionin for three-fourths of a minute, washed in water, dried with blotting paper, and examined.

Counting.—The bottom edge of the smear, where the leucocytes have collected, is located with the low-power lens of the microscope, and when this is arranged in the center of the field the $\frac{1}{2}$ -inch oil-immersion lens is put on. In a properly prepared film from 10 to 20 leucocytes should be seen in one field. The leucocytes should show distinct outlines, their nuclei prominent. A suitable emulsion for most organisms is that in which the leucocytes contain an average of 4 bacteria each. If more than 6 are present the counting becomes extremely difficult and may be inaccurate. The number of bacteria con-

tained in 100 leucocytes is counted, those upon the "patient's" slide and those upon the control slide being enumerated in turn.

The result obtained from the normal is regarded as unity, and the patient's index is expressed as some decimal fraction or multiple of the normal. Thus, if the total number of bacteria ingested by 100 leucocytes in the normal specimen is 310 and the number ingested in the patient's serum is 261, the opsonic index would be 0.71. If the patient's slide showed 480, the opsonic index would be 1.54.

As an emulsion of tubercle bacilli is difficult to prepare, certain technical differences must be taken into consideration. The tubercle emulsion is made from dried and sterilized tubercle bacilli which are first ground as finely as possible in an agate mortar. About 10 "crumbs" of the tubercle bacilli should be used. A single drop of a 1 per cent. saline solution is added to the bacilli and they are ground together. This is suspended in a saline solution amounting altogether to 1 or 2 c.c. The emulsion should be centrifugalized for about one minute to throw down clumps. The supernatant fluid is poured off and put into a second set of sedimentation tubes. This is then placed into an empty test-tube, sealed, immersed in water, and boiled for ten minutes. This tubercle emulsion may be used as a stock emulsion; it may be preserved in the ice-chest for several weeks. For control the serums of two or three normal persons are used separately and an average of these results taken as the normal. Tubercle films should be stained by the Ziehl-Neelsen method.

Modifications of the Wright Tech-

nique.—Some modifications of the Wright method have been suggested. Neufeld and Rimpau (Deut. med. Woch., 40, 1904), working independently of Wright, described substances in the blood-serum of animals immunized to the streptococcus and pneumococcus which they called *bacteriotropins*. They mixed in a test-tube equal volumes of a suspension of leucocytes obtained from the peritoneum or pleural cavity of a guinea-pig, a suspension of bacteria, and diluted immune serum. As a control, a similar mixture was made containing either normal serum equally diluted, or normal saline solution instead of immune serum. The chief difference between this technique and that of Wright is that much larger quantities of each constituent are necessary.

Another method of estimating the opsonic content of a given blood-serum was suggested by Simon, Lamar, and Bispham. These writers employed dilutions both of the patient's serum and of normal serum ranging from 1 in 10 to 1 in 100. With these dilutions they carried out opsonic experiments with bacterial emulsions and washed leucocytes in the same way as is done in the Wright method, except that they recommended the employment of weaker bacterial emulsions than are usually employed in the former method. One of the essential features of the bacteriotropic method of Neufeld and Rimpau is the dilution of the serum, the expression of strength giving the highest dilution, to which a serum may be subjected, and still show opsonic power. Simon, Lamar, and Bispham, in examining their slides, do not estimate the number of bacteria found in the leucocytes, but rather the percent-

age of leucocytes which actually take part in the phagocytic process, that is to say, those which contain bacteria. By the method of dilution they determine what they have called the "opsonic coefficient of extinction." The general opinion of other workers appears to be that the results obtained by this modification are practically identical with the results obtained by the original method of Wright.

Opsonins.—With this technique Wright, with coworkers and students, undertook a systematic study of the relation of blood-serum to phagocytosis. He determined the direct dependence of phagocytosis upon certain substances contained in the blood-serum. He proved conclusively that this serum component acts upon the bacteria directly, not upon the leucocytes, and that it is bound by the bacteria and renders them subject to phagocytosis. This fact of preparing or modifying the bacteria in such a manner that they are rendered easy prey to the phagocytes Wright called an opsonic effect (*opsono*, I cater for; I prepare victuals for), and he employed the term "opsonins" to designate the substances in the blood-fluids which produce this effect.

Nature of Opsonins.—Opsonins are of two kinds: normal opsonins, those which are thermolabile (those destroyed by heating to a temperature of 55° C.), and immune opsonins, those which are thermostabile. It has been suggested that normal opsonins are in reality identical with complement, while immune opsonins are identical with amboceptors (Neufeld and Hüne, Arb. a. d. Kais. Gesund., xxv; Levaditi and Inmann, C.-r. de la Soc. de Biol., 62, 1907). This contention was based not

only on the thermolability of normal opsonins, but also upon the fact that opsonins may be removed from normal serum with the complement by the method of complement fixation. Wright contends that the opsonins have a distinct identity. The observations of Dean and Hektoen appear to support this contention, but the matter is not definitely decided.

The *specificity* of opsonins and their *multiplicity* have been shown by Hektoen and Ruediger (Journal of Infec. Dis., 2, 1905). It has been proved that the opsonic substances may be absorbed from serums by treating them with various species of bacteria, just as specific agglutinins may be absorbed out of an agglutinating serum by the method of absorption. Cold seems to have no influence upon the opsonic power of a serum, but its activity is gradually lost when it is exposed to sunlight.

Source of Opsonins.—As already stated, Metchnikoff believes the leucocytes to be the source of all bacteriotropic substances, while Ehrlich holds that any cell affected by the antigen is capable of being stimulated to produce immune bodies.

Wright believes that opsonins are produced locally at the site of inoculation, and in favor of this cites the fact that when toxins are injected subcutaneously in horses there is a greater production of antitoxin than when the toxin is injected intravenously. Again, patients who show a considerable local reaction at the site of inoculation are apparently immunized more effectively than those who suffer with constitutional symptoms but without appreciable local reaction. There is also the further observation that local immunity

may be acquired and retained apart from the acquirement or retention of general immunity. A local form of immunity illustrating this point is the sensitized conjunctiva. If a weak solution of precipitated tuberculin is dropped into the eye of a normal individual no reaction follows. If after a certain number of days, however, tuberculin is again dropped into this eye there occurs the same kind of a local reaction as if the person were tuberculous. The other eye, on the contrary, shows no change at all.

Sajous, in 1907 ("Internal Secretions," vol. ii, p. 1093), advanced the view that the thyroid and parathyroid glands, which show marked evidences of overactivity in the course of infections, were the original source of the opsonins, which he regards as a component of the normal secretion of these organs. This view has been sustained by the experiments of Marbé (C.-r. de la Soc. de Biol., vol. lxiv, 1908), of the Pasteur Institute, who found that while removal of the thyroid caused a considerable decline of opsonic activity of the blood-serum, the administration of thyroid gland increased it markedly; and also by those of Stepanoff (C.-r. de la Soc. de Biol., vol. lxvi, p. 296, 1909), likewise in the Pasteur Institute, which led him to ascribe "the opsonizing action of thyroid extract to the thyroglobulin of Oswald, which is normally present in the thyroid gland." Sajous's theory harmonizes with all others in the sense that it aims only to show whence the opsonins found in the body cells are originally derived.

Practical Value of Opsonic-Index Determinations.—The question of the utility, value, and necessity of opsonic-index technique was much discussed a

few years ago. This discussion concerned first the accuracy of the method and then the necessity for it. It seems certain that in the hands of a careful, trained technician the method is sufficiently accurate to indicate the relative content of the blood in certain bacteriotropic substances. To prove this a long series of estimations of the opsonic indices have been made. In normal individuals the tuberculo-opsonic index estimations were found to vary from 1.2 to 0.8, the majority of individuals being practically equal, 1.0. This variation is considered normal. "Wild" counts are said to occur occasionally, but as a diagnosis and plan of treatment are not based on a single estimation this objection loses much of its force. Since there are other antibodies in the blood besides opsonins, the question has been raised whether the index may not give a wrong idea of the patient's resistance to certain bacteria. May not the opsonins be low when certain other antibodies are relatively abundant? In answer to this Wright has said that, although there are other antibodies, opsonins are by far the most important. This dictum has apparently not been universally accepted. It cannot be denied that in general the opsonic index follows closely the clinical improvement and increase in the severity of the infection. Wright has consistently maintained that to treat an infection intelligently one must study the course of events following the inoculations of the vaccine by determinations of the opsonic index, and that clinical observations cannot give evidence of sufficient value to constitute a guide for therapeutic inoculation. The whole system of bacterial therapeutics as practised today has been built upon studies

of the opsonic index in connection with inoculations made by Wright and his pupils, and accepted as the guide by them with regard to dosage, intervals between doses, and accessory methods of treatment.

A far more weighty and practically insurmountable objection to the opsonic-index estimations is the time required. In spite of the many good arguments adduced to support his contentions, utilitarianism, if nothing else, has decided upon the negative side. In textbooks published in England and in English medical journals one still reads reports of cases the treatment of which was controlled by opsonic-index determinations, but such reports are rare from any other source. By common agreement in this and other countries it has been decided that clinical control of dosage, of intervals between doses, and of accessory methods of treatment, is sufficiently accurate and reliable for the satisfactory treatment of the great majority of cases. For the general practitioner the necessary laboratory work is too difficult and too time-consuming, and the cost of consultation with a trained bacteriologist would be so great as to restrict vaccine therapy to a very small class of patients.

The technique recommended by Wright and believed by him to be necessary to careful work has therefore been relegated to medical history, while the practical application of bacterial vaccines to the treatment and prevention of disease has gone forward by leaps and bounds. The opsonic index has, however, left footprints in the form of words, to understand the exact meaning of which we must be familiar with the train of events following the inoculation of a vaccine.

BACTERIAL VACCINES.—*Changes which Follow Inoculation.*—

The changes in the bacteriotropic power of the blood which follow the inoculation of a bacterial vaccine were for the first time tested quantitatively upon man in connection with Wright's results in antityphoid vaccination. The work on typhoid was followed by still further researches with regard to the vaccine treatment of Malta fever, tuberculosis, bubonic plague, pneumonia, staphylococcus and streptococcus infections, etc. In all of these the same train of events occurs. After the injection of the vaccine there is a period of diminished resistance which is characterized by a decline in the antibacterial power of the blood. This decline is called the *negative phase*, and it is accentuated and prolonged in proportion to the size of the dose of vaccine injected. If a large dose of vaccine has been used the negative phase may be characterized, clinically, by a rise in temperature and by other constitutional disturbances. If a small dose has been given, the negative phase may be entirely unaccompanied by clinical symptoms. The negative phase is followed by a *positive phase*. Its characteristic is an increase in the antibacterial power of the blood, corresponding to a period of increased resistance. The curve graphically representing the estimation of opsonic indices after inoculation describes a downward course corresponding to a negative phase, then rises gradually to a sharp peak constituting the positive phase, after which it sinks first comparatively slowly and then more rapidly. During the positive phase there is usually a sense of increased physical vigor and improvement in the general symptoms. After the negative

and positive phases of which Wright has spoken as "the ebb and flow and reflow of the tide of immunity," the blood may be maintained for a variable period at a somewhat higher level of antibacterial power than before inoculation, or, as in some chronic and otherwise resistant infections such as tuberculosis, it may go down more rapidly, and in the course of ten days reach the point at which it was before the inoculation.

In the treatment of animals for the production of antitoxins, it is possible by repeated and gradually increasing injections to raise the antitoxic power of the blood to a very high point. At first, it was naturally believed that something of the kind would be possible with the administration of bacterial vaccines; but such an *accumulative effect* in the direction of the positive phase has been found impossible. On the contrary, the opposite condition may arise and must be reckoned with; that is, if repeated excessive doses of a vaccine are given, instead of a slight negative phase appearing after each, the negative phase may be forced down until the patient is in a very serious condition, or death supervenes.

Upon such observations Wright was able to formulate a system of dosage which more than any other single factor was responsible for placing bacterial vaccine therapy upon a practical basis. He was able to show that extremely small doses of killed bacteria were sufficient to elicit an immunizing response of therapeutic value. By means of the opsonic-index method he determined the dosage of bacteria necessary to evoke such an immunizing response. It is true that at the present time we have discarded the opsonic

index as a guide to dosage, but it must be remembered that we have the experience of ten years to guide us. We know now that, except in tuberculosis and possibly certain other infections in which the patient is very weak and toxic, bacterial vaccines are practically harmless. The greatest harm that may follow too large a dose is a severe local reaction resulting in temporary discomfort to the patient.

The *optimum dose* of a bacterial vaccine causes a transient negative phase which, clinically, is scarcely or not at all recognizable, followed by a positive phase coincident with improvement in the symptoms.

Classification of Bacterial Vaccines.

—The vaccine is called *autogenous* when it is made with cultures obtained from the patient's own lesions. *Stock* vaccines are those made of representative types of the organisms in question. In order that stock vaccines may be of the greatest value and have the widest range of efficiency they are generally *polyvalent*, that is, they contain a large number of different strains of the same bacterial species, or the same strain from different sources. Polyvalent vaccines are to be distinguished from *mixed* vaccines, the latter being those containing two or more strains of different species and intended for treatment in mixed infection.

Although it is generally true that autogenous vaccines are of greater value than stock vaccines they cannot, in general practice, be used universally. Furthermore, if an accurate diagnosis has been made, it is only in a relatively small percentage of cases that the autogenous vaccine is necessary. The first consideration that makes stock vaccines a necessity is the cost of the autogenous

product. Only in institutions with well-equipped laboratories can special vaccines be made for each case. In private practice, except in obstinate cases or those of unusual and mixed infections, the expense compels the use of stock vaccines almost entirely. Because of the great variety of their types there are some bacterial species which nearly always necessitate the employment of an autogenous vaccine. This is particularly true of streptococcic and *B. coli* infections. Besides the expense involved there is the consideration of time. In very acute diseases, such as pneumonia and puerperal septicemia, on account of the time required to prepare the autogenous vaccine, the use of a stock vaccine, for the earlier doses at least, is imperative.

Attempts have been made to prepare autogenous tuberculins by an antiformin method, but at the present time the work is too laborious to be of practical value. In this method, the sputum, secretion, or the material containing the organisms is shaken up with antiformin and allowed to stand in the incubator, or at room temperature, for several hours. The antiformin dissolves all bacteria except the acid-fast bacilli. The material is then placed in the centrifuge to throw down the tubercle bacilli. The supernatant fluid is decanted and the sediment is carefully washed two or three times with sterile normal saline solution, after which the tubercle bacilli are spread upon the surface of some suitable medium, such as Dorset's egg-medium, and incubated. A visible growth may be obtained in this way within a few weeks. This growth may be collected and made into a tuberculin. On account of their waxy envelope the tubercle bacilli should

never be used whole, but only after dissolving the wax chemically, or carefully and thoroughly grinding the bacilli in a ball mill.

Gonorrheal rheumatism may be treated with stock vaccines only, unless, indeed, there is a coexistent urethritis. The work of Hamilton seems to show that there is no advantage in using an autogenous gonococcus vaccine. Gonorrheal rheumatism is an example of several conditions which, on account of the difficulty or impossibility of obtaining the infecting organism from the focus of infection, must be treated with stock vaccines. In conditions like chronic posterior urethritis, it is advisable to add to the autogenous mixed vaccine the stock gonococcus culture, even though the gonococcus may not be demonstrable culturally. It is very difficult to isolate the gonococcus at this stage, and it is therefore safer, even though not demonstrable, to consider it present.

DIAGNOSIS.—The diagnosis may be made in four ways: first, by clinical observation and deduction; second, by stained smears; third, by cultural methods; and fourth, by serological reactions. For the general practitioner the first will certainly be the most popular, and in many cases may be considered entirely safe. For instance, the common cause of suppuration in superficial wounds and ordinary furuncles is nearly always the staphylococcus. The predominant organism in yellow pus we conclude to be the *Staphylococcus aureus*, in green pus the *Bacillus pyocyaneus*, etc. Wright has pointed out that in infections above the diaphragm, connected either directly or indirectly with the respiratory passages, the pneumococcus is one of the most frequent

offenders, while below the diaphragm the colon bacillus plays the same rôle.

Diagnosis by the examination of stained smears is the routine procedure in tuberculosis and gonorrhea. The microscope is frequently of assistance in demonstrating the type of pneumonia, of cerebrospinal meningitis, and of a host of other conditions. Up to the present time clinicians have given little thought to organisms other than those reputed to be the causative agent in the condition under examination. Little or no attention is regularly paid to streptococci and staphylococci in the routine examination of sputum for tubercle bacilli. If acid-fast rods are seen the diagnosis is dismissed as positive. Diagnosis by the examination of stained smears is entirely inadequate for mixed infections of all kinds. The vaccine therapist must know all the types of bacteria present in the lesion. Indeed, in not a few mixed infections, after the lapse of two or three weeks, the initial etiological factor has become the least important of the bacteria present. Many failures in the vaccine treatment of such diseases as typhoid fever, influenza, and whooping-cough are undoubtedly due to the fact that this is not recognized. The isolation of the bacteria requires a well-equipped bacteriological laboratory with proper facilities for making the various culture media. The region of the body in which the lesion is located and the type of infection largely determine the particular technique and the culture media to be chosen for the isolation and study of the bacteria; for instance, the isolation of the acne bacillus requires methods very different from those used for the gonococcus.

Blood-cultures.—In blood-cultures

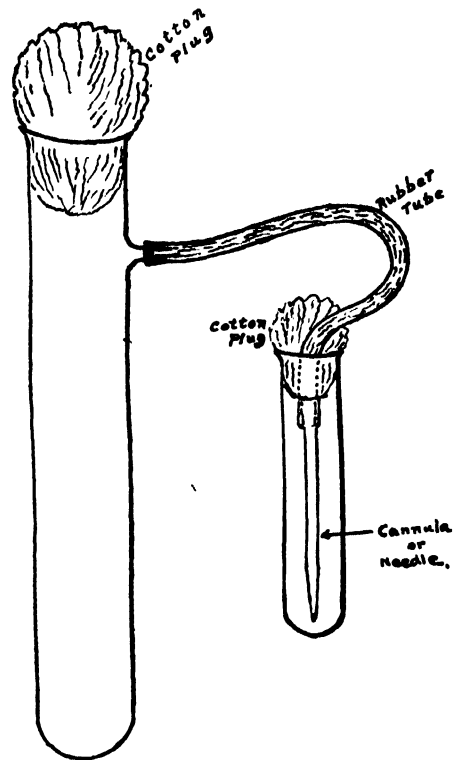
we have a direct and positive method for making a diagnosis; and if the proper technique has been employed, the cultures obtained are pure, and may be used immediately for the preparation of autogenous vaccines.

During the first week of the disease, blood-cultures offer the easiest method for the isolation of the typhoid bacillus. Later, the bacillus disappears from the circulation, and its isolation then, from the feces, is attended with greater difficulty. A high percentage of cases of pneumonia yield, in the early stages, pure cultures of the pneumococcus. In other bacteremias, also in septicemias, and in pyemia, representative organisms are readily obtained by blood-cultures.

The blood is preferably withdrawn from one of the veins at the bend of the elbow, or from the internal saphenous vein as it passes upward in front of the internal malleolus. The skin should be carefully cleansed, first with soap, then with alcohol and ether, and finally painted with tincture of iodine, or 5 per cent. iodine in acetone. If iodine is used the specimen may be taken almost immediately, whereas with bichloride or some of the other antiseptics it is better to wait an hour before beginning the operation. The syringe must be of some sterilizable variety, and, while it may usually be sterilized by boiling for twenty minutes, it is much safer to sterilize it in the autoclave. If the syringe should happen to be contaminated by a spore-bearing organism, boiling, even for an hour, may not destroy the spores. Before placing it in the autoclave the syringe may be put into a test-tube with cotton in the bottom to protect the needle, or it may be wrapped in paper or gauze. If the syringe is of the "all glass"

variety, or if it is a "Record"—which is probably the best for the purpose—it is advisable to sterilize the barrel and plunger separately. Otherwise difference in expansion may cause the barrel to break.

When everything is in readiness a bandage is wound tightly around the



Cannula and side-neck test-tube as used by Noguchi for the collection of blood.

upper arm at about its middle third. This makes the vein stand out prominently and the syringe needle may be inserted easily. It should be pointed toward the shoulder. Great care must be taken to avoid the entrance of air into the vein. In very stout individuals it is sometimes necessary to dissect out the vein. Instead of a syringe one may use an ordinary syringe needle attached

to a rubber tube, leading either directly or by an attached glass tube into a sterile flask. If a syringe is used the blood must be immediately forced out into a sterile flask or into the culture medium. It is preferable to make the culture directly at the bedside, but the blood may be drawn into flasks or test-tubes containing a sterile solution of sodium citrate (1.5 per cent.) or ammonium oxalate (0.2 per cent.) to prevent coagulation. The advantage is that a much greater length of time may be allowed between the withdrawal of the blood and the making of cultures, thus allowing time to transmit the specimen to the laboratory, possibly overnight.

Three flasks of dextrose bouillon should be inoculated with varying quantities of the blood. One of the flasks should contain a very small quantity, so that any antibodies present may be so diluted that they will not inhibit the growth of the bacteria. On account of the high acid production of streptococci and pneumococci, Hiss has recommended the addition of one gram of powdered calcium carbonate to one of the flasks in order to neutralize the acid and permit these cocci to develop.

The best medium for cultures from typhoid patients is a so-called enriching medium composed of ox-bile containing 10 per cent. of glycerin. When this is not available ordinary bouillon seems to give good results. Russell and others have been successful in isolating the typhoid bacillus from specimens of blood obtained from the lobe of the ear. The skin is cleansed in the ordinary way and the blood is received as directly as possible into a sterile Wright capsule. The coagulation of the blood seems to offer no hindrance to the development

of the typhoid bacilli as it does to more delicate organisms. Another great advantage of this method is that the specimen may be sent long distances to the laboratory. Staphylococci and diphtheroid organisms in blood-cultures should be regarded with considerable suspicion, since they often occur as skin contaminations. This is especially true of *Staphylococcus albus*, but even when a *Staphylococcus aureus* is obtained a corroborative culture should be made. If after twenty-four hours an uncontaminated growth is found in the bouillon culture, the autogenous vaccine may be made directly from it without further manipulation. But the evidence that the culture is pure must be unquestionable.

Collection of Infectious Material.—For the collection of infectious material from various parts of the body for diagnosis and for the isolation of the various bacteria present in the lesion, expensive and unusual apparatus is entirely unnecessary.

Because of the possible differences in rapidity of growth and other biological characteristics of the bacteria, it is advisable to submit to the laboratory for examination a smear upon a microscope slide, a culture made directly from the patient, and a specimen of the infectious material in a sterile tube. It is sometimes best to send infectious material dried on a sterile cotton swab. As a rule, the bacteria remain alive in the dried state, and there is no danger that the more vigorous will overgrow the more delicate. An outfit answering all these requirements may be easily placed in a small mailing tube. Infectious material, cultures, etc., when sent through the mails should be put in a double tube made of tin and heavy

PLATE I.

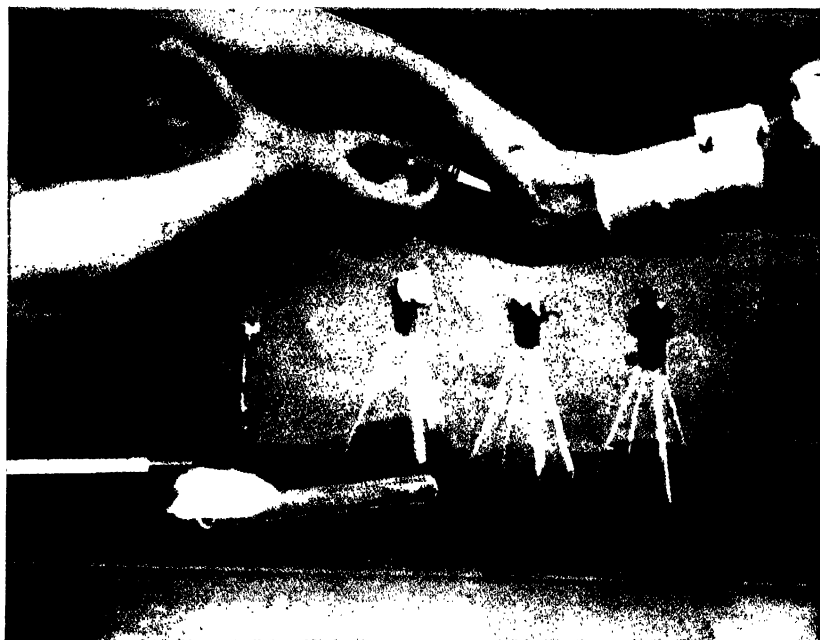
Fig. 1.

Blood-cultures.—Withdrawing blood from vein at bend of elbow. One flask contains a large amount of bouillon, one a small amount, and one bouillon with chalk.

Fig. 2.

Washing Sputum.—Right. With sterile forceps, a little mass of the sputum is shaken successively in six flasks containing sterile saline solution.

Inoculating Blood-agar Plate with Glass Rod.—Left. For the isolation of the bacteria, the washed sputum (or a tiny drop of culture pus, urine, or other infectious material) is placed upon the surface of the blood-agar and smeared carefully over the whole surface with a sterile glass rod.



successful in collecting bronchial secretions from children by using a mouth-gag and touching the pharynx with a cotton swab. This causes the child to retch, when the material is brought forward and projected against the swab. One should never attempt to collect material from the mouth or pharynx without the use of a tongue-depressor. When the specimen is to be collected from the conjunctiva there should be no preliminary cleansing, as this might wash away the few bacteria present. To collect pus from the male urethra cleanse the glans and insert the end of the pipette into the meatus; if no pus appears the urethra may be stripped forward. The female urethra is easily stripped by inserting the index finger into the vagina; press on the upper wall and gently bring the finger forward while the labia are held apart. The uterus should be pulled down with a tenaculum when a specimen is to be collected from the cervix or a sterile cylindrical speculum is inserted into the vagina. Never allow the swab to touch the sides of the speculum or to enter the uterine cavity. The danger of carrying infection into it is so great that no risk may be taken. Soiling the outside of the tube or container with infectious material is especially to be guarded against; the infection may be due to an extremely virulent organism of a particularly dangerous or epidemic disease. Should there be any suspicion that the tube has been thus soiled it should immediately be flamed or burned, boiled, or soaked in a strong antiseptic.

Culture Media.—The best general culture medium for the isolation of pathogenic bacteria is blood-agar. If there are no other facilities at hand for

obtaining blood, a small amount, sufficient for several tubes or plates of agar, is easily obtained by pricking the finger. After winding a bandage around it, it is carefully cleansed and pricked just back of the nail with a sterile needle or sharp glass point. The blood is collected directly in a capillary pipette and then transferred to the culture medium, or it is allowed to drop directly into the tube. If this is done with ordinary care there is little danger of contamination. Small quantities of blood may be obtained from the ear-veins of a rabbit and used in the same way. For larger quantities it is more convenient to bleed an anesthetized rabbit to death, allowing the blood to flow through a sterile cannula into a flask containing glass beads. The flask is occasionally shaken while the blood runs in, and the shaking is continued until the fibrin has formed, the beads serving to defibrinate the blood. The results are generally very satisfactory. Human corpuscles are usually considered preferable, but the corpuscles of the horse, sheep, goat, calf, or rabbit are a satisfactory substitute.

For isolating organisms upon blood-agar it is best to use Petri dishes, those with porous tops being generally preferable. About a cubic centimeter of defibrinated blood is added to a tube of melted agar which has been cooled to between 40° and 45° C. After thorough mixing this is poured into the Petri dishes. Since the blood-agar plates should always be incubated twenty-four hours before they are used, it is advisable to have a stock always on hand. They may be preserved in the refrigerator for some time without deterioration. For inoculating these plates, a drop of the infectious material is placed on the

surface of the culture medium and is smeared well over the entire surface with a sterile glass rod. This same rod is then smeared over the surface of a second, third, and sometimes a fourth plate. This procedure serves to so dilute and spread the bacteria in the infectious material that after twenty-four hours' incubation single colonies may be easily fished from the third or fourth plate.

Instead of plating the material directly it is sometimes advisable to shake a small quantity in a tube of bouillon or sterile salt solution and transfer a drop of this fluid to the surface of the Petri dish, especially if the material has been dried. In this case, it is also sometimes of advantage to incubate the tube of bouillon for a few hours before making the smears upon the plates.

Allen (Journal of Vaccine Therapy, vol. i, No. 1, January, 1912) gives the following directions for the *isolation of the acne bacillus*: "For the cultural examination the following materials are necessary: Two plates of agar-agar, two plates of medium of the following composition: Agar-agar 3 per cent., to which has been added while fluid an equal part of a mixture of pure oleic acid and ascitic fluid or of ox-blood serum, and sufficient saturated solution of neutral red to tint the whole a bright red, the whole being thoroughly mixed before being poured into the Petri dish; also four or five tubes of peptone broth, and a suitable apparatus for anaërobic incubation. Personally I find a glass cylinder eight inches high and four inches in diameter all that is needed. A mixture of saturated aqueous solutions of caustic soda and pyrogallie acid is poured into the cylinder for a depth of two or three inches, the

culture tubes placed inside, and ~~air~~ excluded by means of a good cork, over which melted paraffin is poured. Sebum from non-pustular and secretion from pustular foci are distributed over the various plates and mixed with the peptone broth. All the plates and one or two of the tubes are incubated aërobically at 37° C. for twenty-four to thirty-six hours, while the remainder of the tubes are subjected to anaërobic culture in the above apparatus. Sometimes both the acne bacillus and the staphylococcus can be secured with ease in pure culture from the plates; should colonies of the former, however, fail to appear, then the anaërobic incubation of the tubes should be continued for about a fortnight. After this interval most of the staphylococci will have died, whereas the acne bacilli will have multiplied. By inseminating a loopful or two of the well-mixed broth upon a plate of the oleic acid-serum-neutral red medium and incubating aërobically for twenty-four hours discrete colonies of the acne bacillus will be readily obtained and be available for planting upon slopes or plates of the above medium. Should staphylococci have been present in the various foci, no difficulty whatever will be experienced in their isolation from the agar plates after twenty-four hours' aërobic incubation."

For the *isolation of the gonococcus* the medium of choice is a neutral agar containing ascitic or hydrocele fluid. Human blood-serum is valuable, but more difficult to obtain. The medium is greatly improved by adding 5 per cent. glycerin or 1 per cent. dextrose. The gonococcus is extremely delicate and its isolation cannot be successfully accomplished if the pus is allowed to become chilled. The smears on the

plates must therefore be made as quickly as possible and the plates placed in the incubator.

Plates inoculated in this manner are removed from the incubator and isolations made after twenty-four hours (colonies fished should be marked with a blue pencil upon the bottom of the plate), after which they may be re-incubated for another examination at the end of forty-eight hours. The colonies present are studied with an achromatic triplet lens, or, better, with a binocular microscope. Several of each type found are transferred by means of a sterile platinum wire to suitable media in tubes. A tube containing a solid medium and a tube of bouillon should be planted from each colony. Here again blood-agar is the best solid medium for general use. If the colony closely resembles a staphylococcus, or *B. coli*, ordinary agar is entirely sufficient. Blood-agar is especially valuable for the isolation of the pneumococcus, the influenza bacillus, and members of the catarrhalis group. It is also of some value as a differentiating medium for the pneumococcus on account of the peculiar manner in which the pneumococcus colonies take up the pigment. If the colony fished stood alone the resultant subculture is likely to be pure. After twenty-four hours' incubation, a microscope slide should be made from each culture and stained by Gram's method. For a tentative diagnosis, the relations and grouping of the bacteria may be studied more satisfactorily from a bouillon culture. This preliminary identification is generally sufficiently accurate for practical purposes. The ultimate identification and classification according to species and variety constitute a much more extensive and com-

plicated procedure. In considering the isolated bacteria for the preparation of a vaccine, the thing of paramount importance is to be certain that they are not spore bearers. If there is any doubt upon this point it is better to omit the organism from the vaccine until a definite decision can be made, because, as the vaccines are prepared at present, the method of sterilization is not sufficient to destroy spores. Even though the check tests may be made with the greatest care there is a chance that any spores present may not find suitable conditions for rapid development, and thus escape detection.

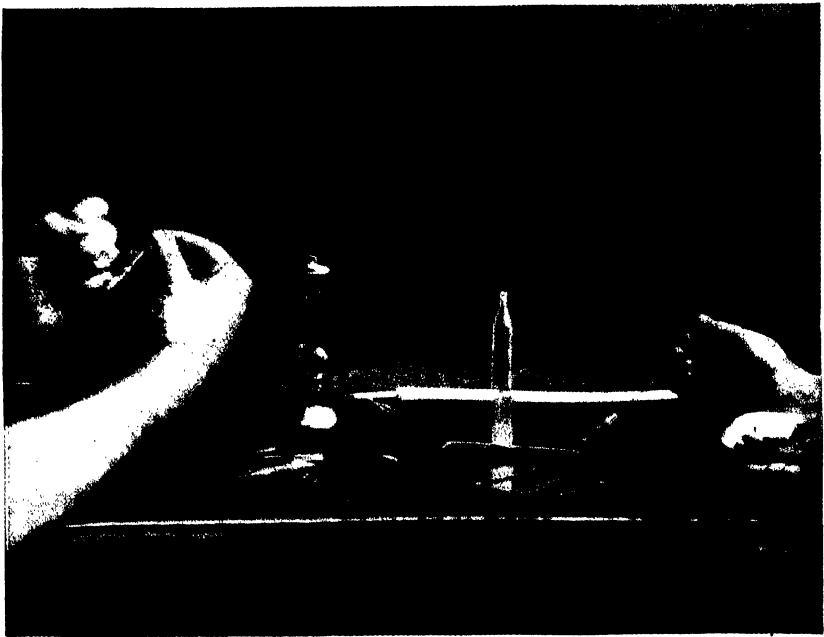
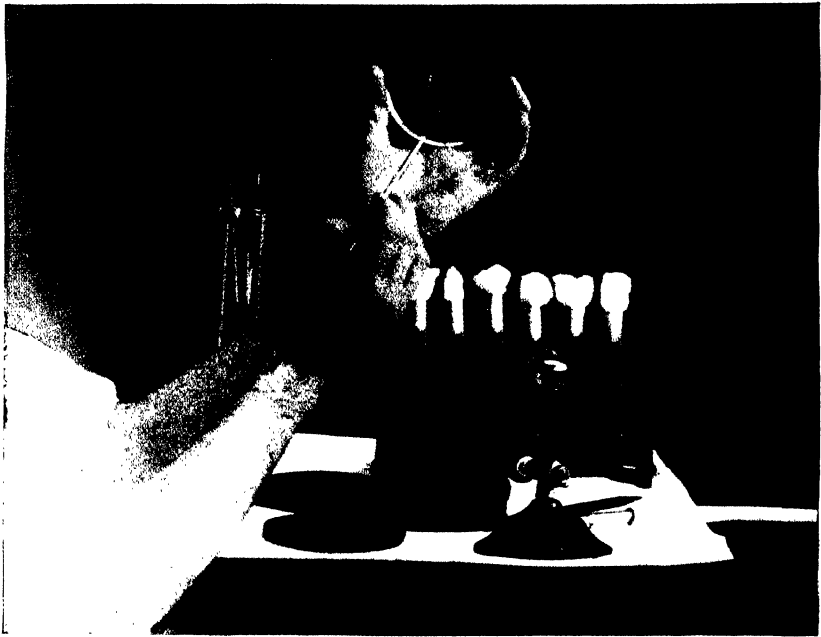
Upon the evidence gained from an examination of the slide made from the bouillon culture and stained by Gram's method, we are able to classify the cocci with a high degree of accuracy. Gram-positive cocci in irregular groups may be considered staphylococci; the color of colonies upon agar will tell whether they are "aureus" or "albus." The *Staphylococcus pyogenes citreus* so seldom occurs that it need not be considered a distinct variety. Liquefaction of gelatin will further help to differentiate between pyogenic and non-pathogenic species. The pyogenic strains liquefy gelatin. If Gram-positive cocci occur in tetrads they are likely to be the *Micrococcus tetragenus*; the sarcina occurs in cubes or packets. Bezançon has called attention to the *M. paratetragenus*, which is said to appear on the slide as Gram-positive cocci with a background of Gram-negative cocci. Cocci occurring in chains are likely to be streptococci, although pneumococci may and often do grow in chains. The demonstration of a capsule, after passing the cultures through a mouse, and the lanceolate shape are decisive in

PLATE II.

Fig. 1.

Collecting Isolated Colonies from Blood-agar Plate with sterilized platinum wire.

Collecting Specimen of Blood in Wright Capsule.—Left. Mixing Equal Parts of Blood from Finger and Bacterial Suspension in Capillary Pipette.—Right. The sealed tube standing upright upon a block of "plasticine" contains the thick suspension of bacteria. After counting, this will be diluted with saline solution. The small tube standing slanted in the plasticine contains a sample of the thick suspension, removed for counting. The pipette contains a column of blood, and an equal quantity of the thick suspension is being taken up.



immunizing power as have the whole germs.

A piece of glass tubing, about three-eighths inch in diameter and four inches long, is heated in the Bunsen or blow-pipe flame, about its middle, until the glass is well softened, then it is withdrawn from the flame and pulled out carefully so as to draw the tubing down to capillary fineness. It is then cut with a file so that the ends of the original tubing have connected with them a capillary stem about six inches long. With a blue-wax pencil a mark is made on the capillary stem one-half to five-eighths inch from its extremity. A rubber teat is fixed on the larger end. This tube is to be used for measuring and mixing equal parts of blood and bacterial suspension. The sealed tube containing the bacterial emulsion is marked with a file and the upper part cracked off carefully. A small quantity of the thick suspension is drawn up into the larger part of a sterile capillary tube such as that just described, the capillary end of which is then sealed in a small flame, thus making a tiny cup containing a sample of the suspension. The tube containing the suspension is resealed. A bandage is now wrapped around the thumb or middle finger, which is pricked just back of the nail. By gently manipulating the rubber teat, then dipping the end of the capillary pipette in the drop of blood, it is filled exactly to the mark made by the wax pencil. The end is then removed from the drop of blood, carefully cleansed, and a tiny bubble of air allowed to enter; the end is then dipped into the suspension of bacteria and a volume of the suspension equal to the volume of blood is drawn in. The blood and bacterial suspension are then forced out on

a microscope slide, drawn up into the tube, and again forced out. This procedure is repeated until the blood and bacterial suspension are thoroughly mixed. Small drops are then placed on clean slides, and with the edge of a second slide the mixture is spread evenly in thin layers. The film is allowed to dry in the air, is fixed by heat or wood alcohol, and stained by methylene blue, diluted fuchsin, or Wright's stain. Under the microscope the red blood-corpuscles and the bacteria are seen evenly distributed. The number of each is counted and the figures set down in separate columns. Enough fields are counted to equal about 500 red corpuscles. The number of red corpuscles in 1 c.c. of the blood of the operator being known, and the ratio between the corpuscles and bacteria being ascertained by this enumeration, it becomes a simple mathematical problem to calculate the number of bacteria per cubic centimeter. For example, if the number of corpuscles in the fields examined equals 500 and the number of bacteria in the same fields equals 1000, then a cubic millimeter of the emulsion contains 10,000,000 (as 500 is to 1000, so is 5,000,000 to 10,000,000). This supposes that the blood of the person making the count contains 5,000,000 red corpuscles per cubic millimeter. It is advisable to corroborate this figure by one of the well-known methods of enumerating red corpuscles.

Sterilization of the Thick Emulsion.

—After the small sample has been removed for counting and the tube containing the thick emulsion has been sealed again, it is immersed in a water bath and kept at a temperature of 56° to 60° C. for from one-half to one hour, according to the variety of the organ-

PLATE III.

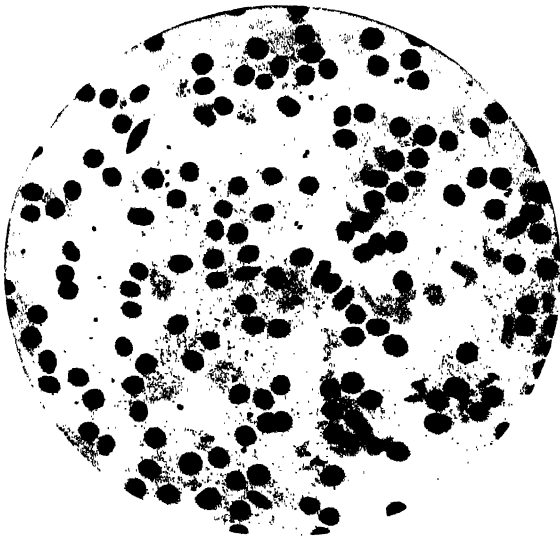
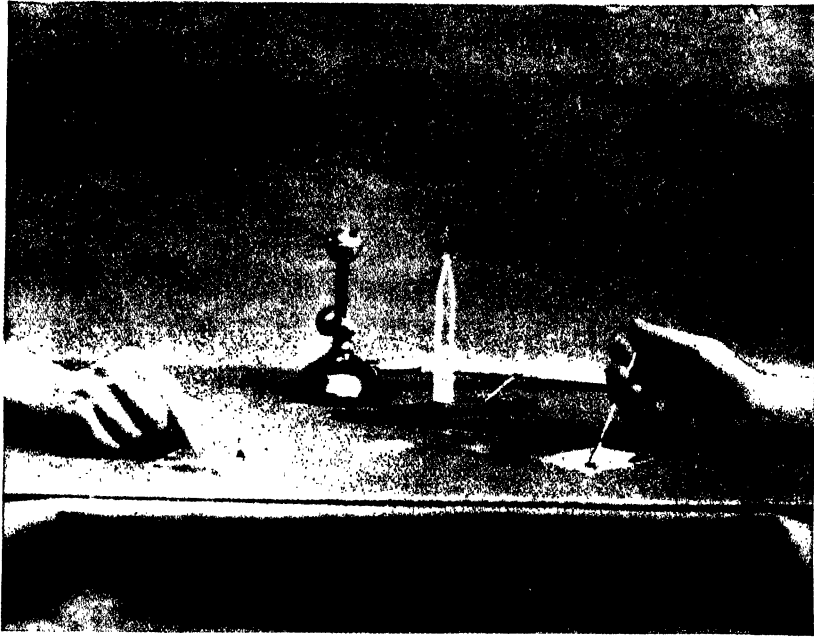
Fig. 1.

Mixing the Blood and Thick Suspension.—Right. The two columns in the pipette are forced out on a clean slide and drawn up again into the tube by gentle manipulation of the rubber teat. This is repeated several times.

Making the Smear upon the Slide.—Left. After thorough mixing, a drop of the mixture is placed on a clean slide near its end. This is then spread evenly by drawing the edge of another slide over it. The smear is then fixed and stained.

Fig. 2.

Red Corpuscles and Cocci Spread on Slides.—Microscopic examination for counting bacteria in relation to the corpuscles.



-isms. For killing the bacteria the tube containing the thick suspension must be sealed and *entirely immersed* in the water. It has been determined that if an antiseptic is added to the suspension before it is sterilized the specific proteins are altered so that the vaccine is much less potent. For this reason, the degree of heat and the length of the exposure are usually diminished to the minimum commensurate with safety. Certain organisms, such as gonococci, pneumococci, and the influenza bacilli, are sometimes not heated at all, the antiseptic being depended upon for sterilization. This procedure is not safe, however, for such vigorous organisms as staphylococci and certain strains of streptococci. After removal from the water bath, the tubes are opened for the removal of their contents and the dilution of the vaccine. Before the dilution is made, subcultures upon a suitable medium should be made to determine the sterility of the thick suspension.

Diluting the Vaccine.—The next step is to dilute the thick suspension sufficiently to make each cubic centimeter contain the desired number of bacteria. The diluent is generally sterile physiological saline solution (0.85 per cent. sodium chloride) containing 0.25 per cent. tricresol, 0.5 per cent. phenol; or 0.25 per cent. liquor cresolis comp. The amount of diluent to be mixed with the thick suspension in order to obtain the desired strength is a simple mathematical problem. Staphylococcus suspensions are diluted so that 1 c.c. of the completed vaccine will contain about 300,000,000 cocci per cubic centimeter and other bacteria, so that each cubic centimeter will contain about 50,000,000. These figures are arbitrary and

the strength may be adjusted to suit the individual preference of the immunizer. Mixed vaccines are made in exactly the same way except that the mathematical calculation of the amount of each thick suspension required to be added is made separately.

Test for Sterility and Safety.—The tests for harmlessness and sterility are of more importance than any other factor in the preparation of the bacterial vaccine. Substances intended for injection beneath the skin must be prepared with infinitely more care than those intended for oral administration. Extremely dangerous substances taken by mouth may generally be recovered or their effects neutralized by well-known means, but when a harmful or infected substance has been injected beneath the skin it is impossible to recover it. Relatively few of the pathogenic bacteria are able to resist the germicidal action of the gastric juice, but the subcutaneous tissues are susceptible to practically all of them. Our tests then must assure us that the vaccine contains no substance poisonous or harmful in itself, and they must demonstrate the absence of all living bacteria and spores.

The subcultures from the completed vaccine are therefore of paramount importance. The medium on which they are made must so dilute the preservative that its direct antiseptic action can have no influence upon the development of any living bacteria or spores that might be present. For this reason subcultures on agar or other solid media cannot be used; they must be made into a suitable *fluid* medium. Furthermore the subcultures must be made under conditions which will favor the development of anaërobic bacteria and spores as well as aërobes, because the most

dangerous organism that may gain access to the vaccine is an anaërobe and a spore producer. This organism is the tetanus bacillus, and it is so ubiquitous that it must never be considered absent without proof. Then a culture medium in a tube or vessel which will favor the development of the tetanus bacillus should be suitable for subcultures from bacterial vaccines. Bouillon in ordinary fermentation tubes seems to answer all requirements. The tetanus bacillus will develop readily in a fermentation tube containing preferably 1 per cent. dextrose bouillon, provided it has been freshly sterilized. Under these conditions the closed arm is sufficiently protected from air to favor the growth of anaërobes.

As to whether or not tetanus spores might develop, any doubt is removed if a small piece of guinea-pig liver or heart tissue, as recommended by Theobald Smith, is crowded into the bend of the fermentation tube. The fermentation tube subcultures must be incubated at least forty-eight hours before an opinion may be given as to whether or not the vaccine is sterile. The naked-eye appearance of the tube is not sufficient, because the growth of tetanus and any flocculent material at the bend of the tube must be studied under the microscope.

The "Short" Method.—For reasons possibly best known to those who are engaged in such practice there has been developed a technique which is mentioned only to be condemned. This is the so-called "short" method of preparing autogenous vaccines. It may not be sanctioned except for cases such as puerperal septicemia, when it is of the utmost importance to obtain a vaccine of some kind within the shortest pos-

sible space of time. Under such circumstances cultures are made directly from material containing the infecting organism and incubated overnight. If the culture is in bouillon the bacteria are counted and the culture is heated to 60° C. for one-half hour, diluted with normal saline solution, the antiseptic added, and the vaccine used forthwith. If the culture has been made on agar the growth is suspended in normal saline solution and then treated as a bouillon culture. It is never *safe* to use a vaccine without first testing it for harmlessness and sterility, but it must be recognized that there are times when we must choose between two evils. This short method may be applicable when pure cultures are obtainable from the blood, as in streptococcus and pneumococcus septicemia, and in the cases of furunculosis, when there is only a staphylococcus present. It should be recommended in any case where there is a mixed infection or where it is at all possible that extraneous organisms may have entered during the collection of the infected material. It should never be used for making autogenous vaccines from sputum, urine, ulcers of various kinds, or suppurating sinuses.

Vaccine Containers.—The most convenient container for autogenous vaccines or those made extemporaneously in small amounts is the bottle fitted with a rubber cap devised by Wright. The capacity of the bottle is from 20 to 30 c.c. It is plugged with cotton and sterilized in an oven by dry heat, the rubber cap being sterilized in the autoclave or by boiling for twenty minutes in 0.2 per cent. carbolic acid or tricresol solution. After pouring the vaccine into the bottle or running it in through a pipette the rubber cap is stretched

over the mouth of the bottle. The advantage of the rubber cap is that with a needle of small caliber vaccine may be withdrawn from the bottle without removing the stopper, thus avoiding considerable risk of contaminating the vaccine. The cap is first wiped with liquor cresolis comp. or phenol, the needle of the syringe is plunged through the rubber, the bottle is turned upside down, and the vaccine is withdrawn into the syringe. After the withdrawal of the needle the rubber closes automatically and no further procedure to protect the vaccine is necessary.

Inoculation, Site of.—The site to be selected for making the inoculation may be important. Acting upon the theory that opsonins are produced locally, attempts have been made, in certain obstinate conditions, to inject up-stream with regard to the focus of infection, the supposition being that the newly liberated antibacterial substances are thus carried directly to the focus of infection by the lymph as it drains through it. In this manner the antibacterial substances might be expected to come into application in a concentrated condition.

This, however, is practically not often taken into consideration. At the present time the vast majority of injections are subcutaneous into the arm near the insertion of the deltoid muscle. It is sometimes more convenient to vaccinate women in the suprascapular region because this point may be reached by merely loosening the dress at the back of the neck. Many physicians prefer the inner surface of the forearm below the bend of the elbow.

Technique of Injection.—It is advisable to scrub the site of injection with soap and water, followed by alco-

hol and ether, or, an area of the skin about the size of a five-cent piece may be painted with pure lysol, tincture of iodine, or 5 per cent. solution of iodine in acetone. If lysol is used the excess must be wiped away after the removal of the needle.

Reactions.—At the point of injection there usually appears within a few hours an area of redness. This persists for twenty-four to forty-eight hours or longer, according to the size of the dose and the susceptibility of the patient. Following a very large dose some constitutional disturbance is not infrequent. This consists of pains in the back and limbs, headache, and possibly slight fever.

Accessory Methods of Treatment.—In the opinion of the writer the most important chapter contributed to our knowledge of therapeutic inoculation by Sir Almroth Wright is not that concerning opsonins and the determination of the opsonic index, but that concerning the methods by which such antibacterial agencies as the patient may already possess or may acquire by immunization may be used by the tissues for the destruction of microbes at the focus of infection. Not infrequently the opsonic index of the patient before treatment is as high as the immunizator may reasonably expect it to be after treatment, and yet the infection continues as though there was a poverty of bacteriotropic substances in the blood. If such occurs without vaccine inoculation it is likely that the same conditions are responsible for those cases in which inoculation fails to benefit the patient even after treatment has been continued sometimes for months. We know that the parenteral introduction of foreign proteins into animals, except in the

rarest instances, *must* be followed by the production of specific antibodies. If, then, the newly formed antibodies which the patient certainly possesses are not exerting any influence whatever upon the infectious process, the failure is due to conditions which prevent the bacteriotropic substances from coming in contact with the infective elements. The writer believes he may be pardoned for using this paper freely in the following:—

“On Some Points in Connection with Vaccine Therapy and Therapeutic Immunization Generally,” Practitioner, May, 1908; reprinted in “Studies on Immunization,” Wright, New York, Wood, 1910, pp. 452-465.

Where inoculations are undertaken for prophylactic purposes the immunizer is not required to make any disposition for bringing the antibacterial elements of the blood fluids and the phagocytes into application upon invading microbes. Exactly the same thing holds true in vaccine therapy where the bacteria have not yet effected any fundamental changes in the invaded tissues. But where they have already gained a foothold and profoundly modified local conditions the situation is entirely different. It is then necessary not only to increase and maintain the antibacterial power of the blood, but also to take special steps to bring the phagocytes and antibacterial elements of the blood into contact with the invading micro-organisms.

In the circulating blood the body has at its immediate disposal the entire bacteriotropic substances contained in the plasma as well as its whole force of phagocytes. On the contrary, when the bacteria effect an entrance into the tissues they find opposed to them only

such stray phagocytes as may be casually passing through the tissue spaces and only that amount of antibacterial substances which is contained in the lymph that flows through these particular tissue spaces. If this statement needs support it is necessary only to point out the fact that blood infections are of rare occurrence compared with localized infections, which are common. It is quite clear that the aim and object of our treatment ought to be to equalize conditions in the infected tissue and in the circulating blood.

Inflammation is evidence of an attempt to preserve the immunity of the tissues: first, by the transfer of phagocytes, and, second, by the transfer of antibacterial fluid from the circulating blood to the invaded tissues. Whenever this effort fails changes in the tissues occur which hinder the effective access of phagocytes and bacteriotropic substances to the infecting microbes. The result is the establishment of a focus of infection which is specially favorable to the invading bacteria. The impediment may consist of a defective blood-supply to the seat of infection, hypercoagulable and hyperviscid condition of the blood, accumulation of excessive fluid in the focus of infection, or plugging of the tissue spaces by accumulated leucocytes and coagulated lymph. In the latter case the gradual reduction of the antibacterial potency of the lymph renders the phagocytes ineffective and the accumulation of bacteriotoxins and tryptic ferment paralyzes them.

In the case of an excess of serous fluid about the focus of infection it is obvious that the poverty in phagocytes tends to retard the destruction of bacteria; the bacteria gradually absorb the bacteriotropic substances from the fluid,

which then becomes less potent in antibacterial power. In the reverse condition the tissue spaces are plugged with leucocytes and with coagulated lymph, in which case we have a preponderance of phagocytes over fluid elements. This hinders the conveyance of any additional lymph or of any reinforcing phagocytes to the focus of infection. When an infection goes to the point of suppuration, disintegration of the leucocytes liberates in the focus of infection increasing quantities of a tryptic ferment overpowering the normal antitryptic power of the lymph. The fluid pus becomes definitely tryptic and immediately surrounding tissues are rapidly dissolved, with the result that a sac is formed and definite fluctuation is obtained. It is clear that if fresh phagocytes should be brought to the scene there would be no opsonins to assist them and no benefit could result. The outflow of lymph from superficial vessels, associated with the inflammatory reaction to a superficial infection, is staunched when the lymph begins to coagulate and is definitely arrested when it desiccates and hardens into a scab. Any phagocytes which may be contained in such lymph are first immobilized and then killed by drying. On the other hand, bacteria which are not killed by drying are sheltered from the attacks of the phagocytes. These have the opportunity of multiplying in the deeper and correspondingly moister layers of the scab, where they reduce the antibacterial power of the comparatively stagnant lymph and may then be in a position to invade the underlying subcutaneous tissue or epithelium and thus extend the area of infection. In a sinus which is freely discharging pus the conditions are

similar to those in an abscess. The pus possesses a low opsonic power, it contains no effective leucocytes, it may be charged with bacterial toxins, and it contains a tryptic ferment. A sinus which is not discharging presents a condition somewhat comparable to that of a well in which the inflowing water has deposited on its walls an insoluble element which chokes all the conduits of inflow. Upon the walls and floor of such a well forms of life may quite well maintain themselves as they could not against a copious inflow of water. So in a dry sinus the density of the granulation tissue lining it prevents free outflow of lymph upon the surface.

There are two measures which may aid in overcoming the conditions that prevent the access of the leucocytes and bacteriotropic substances of the blood to the infecting elements. The first of these comprises those measures which may be employed to stimulate the egress of antibacterial agencies from the blood; the second, those measures which may be employed to open the way for the entrance of the antibacterial substances and phagocytes into the actual focus of infection.

An increased blood-pressure favors the egress of the antibacterial substances. Where the focus of infection is so situated that its blood-supply can be controlled the arterial circulation may be increased and the venous circulation impeded. The capillary pressure may be raised by the application of heat in any form or by rubefacients. Bier's method of applying a bandage to the limb is also advised. In dealing with the question of raising capillary pressure two considerations must be kept in view. On the one hand, the question as to whether the normal

blood-supply to the infected part is capable of furnishing an adequate lymph-stream must be considered; on the other hand, we must weigh the advantage which would be derived from the determination of increased protective substance of the infected part against the disadvantage which might result from the fact that the ampler lymph-stream would carry into the blood bacterial products which were previously locked up in the focus of infection—*autoinoculation*. In many cases this is a question which cannot be resolved without a trial supplemented by a series of blood examinations. In general it may be said, however, that the greatest advantage will be where the bacterial focus is situated in a poorly vascularized tissue and that the disadvantage will be least (*a*) in the earlier stages of an infection, (*b*) where the bacterial focus is of strictly moderate dimensions, and (*c*) where it has just been evacuated. In the case where the dimensions of the bacterial focus are considerable the disadvantages of determining an increased lymph-stream to the affected tissues will generally altogether outweigh the advantages.

Wright has pointed out that a condition of diminished coagulability is associated with increased transudation into the tissues and that a condition of increased blood coagulability is associated with restricted transudation of the lymph which is very prone to coagulate in the tissues. He has further shown that the blood may be made more coagulable by the administration of calcium salts or may be diminished in coagulability by the administration of a decalcifying agent, such as citric acid (citric acid, 2 to 4 grams, t. i. d.). These points come into application, the

former in cases where there is constant autoinoculation when the administration of calcium salts are sometimes of decided benefit. On the other hand, the administration of citric acid has proven a very important addition to the treatment of brawny swelling. Wright (Lancet, Aug. 24, 1907) has given the details of a case of Ludwig's angina, in which citric acid was the sole remedy necessary to bring about a rapid recovery from the infection.

Among the measures which may be employed to open the way for the entrance of antibacterial elements in the focus of infection there may be considered evacuation by incision, evacuation by aspiration, evacuation by puncture or incision combined with cupping, evacuation by puncture, or incision; or removal of scabs combined with the local application of a chemical lymphagogue.

Evacuation by incision is the usual surgical procedure for the treatment of any focus of infection in which pus is present. Practically the only thing desired by the surgeon is the evacuation of the pus, and if no pus is found incision is considered useless. Notwithstanding this the chief value of the incision is that by the evacuation of the pus antibacterial agencies of the blood may be brought into effective operation upon the tissues surrounding the abscess cavity. For the incision to be of the greatest benefit, then, the opened wound should be used to induce a flow of lymph through the infected tissues.

The danger of secondary infection in an incised wound and the resultant sore would make one hesitate and attempt to find a better method for the evacuation of the pus. In general all requirements are satisfied by aspiration. An

ordinary syringe needle is inserted into the abscess cavity and the fluid pus removed. An equivalent of drainage can be obtained by repeated aspirations.

Bier and Klapp have recommended a method of evacuation by incision or multiple puncture combined with cupping. At first sight this method would seem to furnish exactly the forces any immunizator would wish to employ for evacuating the inflammatory products from choked tissues and for drawing out the blood and carrying from the infiltrated tissues a stream of immunizing lymph. One requisite to success has been overlooked. In reality this procedure is a filtration process carried out with the help of an exhaust. It will be clear that, where a viscid and coagulable fluid has to be drawn through a very fine system of pores, the clothing of the fluid in or at the mouths of these pores may very readily bring the filtration to a standstill. In the case of a laboratory experiment the filter, if it is a paper filter, will then bulge and give way. In the case of the animal tissues, in like manner, even when the negative pressure is kept within strict limits, inevitably something will give way. What will in point of fact give way will be the delicate capillary walls, and in the case of a carbuncle thus treated its last state is, according to Wright, worse than its first.

To continue with the illustration of the filter: If we can clear the surface of it (as by the removal of scabs from an infected surface) or pierce through the surface layer of the filter (as by incision or puncture into a focus of infection), and if we can then without the application of any violence cause the fluid to well out through the pores, at the same time depriving that fluid of its

coagulability, we shall then gradually open up and keep open the choked filter.

In a hypertonic salt solution containing sodium citrate we have a chemical agent which will, when applied to the surface of an open system of tissue spaces, cause a lymph-stream to flow outward through these tissue spaces toward the surface, while it will, at the same time, deprive that lymph of its coagulability. Such a solution consists of 5 parts of common salt and $\frac{1}{2}$ part citrate of soda dissolved in 100 parts of boiling water. Sometimes a concentration of 1.5 to 2 per cent. of salt containing the same amount of citrate will be preferable. Where incisions have been carried down in the infiltrated tissues, lint soaked in the stronger solution may with advantage be put in the wounds. Sinuses *should* be syringed out with the same lotion, a piece of lint soaked in the lotion being afterward introduced into their orifices.

The skin in the neighborhood of the orifice is protected against the irritating effect of the brine by a coating of vaselin.

After a wound has in this way been sufficiently washed with a stream of immunizing lymph, it will be well to stanch the lymph-flow by powdering the surface with a styptic powder consisting of calcium chloride 1 part, precipitated chalk 400 parts.

Dosage.—It was first believed that one of the most important things to be settled before practitioners could use bacterial vaccines in their work was the matter of dosage. This was apparently based upon the belief that as much harm might be caused by an overdose of a bacterial vaccine as had been shown by experience to be pos-

sible from the injudicious use of tuberculin. Wright probably led in this feeling and arrived at his conclusions as a result of observations upon the negative phase. It is true that in patients who are extremely ill and suffering from conditions associated with profound toxemia or bacteremia only minimal doses should be administered; but in sthenic types of disease the greatest harm that might be done appears to be a transient increase in the severity of the local condition, with subsequent benefit. In other words, experience has shown that, in general, bacterial vaccines are harmless. Metastatic foci of infection have not resulted from overdoses, and there is no record of a single instance where serious harm has been done by the use of bacterial vaccines. Leary (Boston Medical and Surgical Journal, vol. clxi, p. 714, 1909) has reported 2 cases which through an error received 10 billion dead staphylococci at a single dose. No ill effects at all were noticed in one; the other, however, collapsed a few hours after the inoculation, but responded to strychnine and the application of hot-water bags and had practically recovered from the immediate effects of the dose within fifteen minutes.

It is the consensus of opinion that for subsequent doses the clinical symptoms following the initial injection give a sufficiently reliable guide. The important point about dosage to be determined, then, is the size of the initial dose. As noted in the clinical section of this article, there is little uniformity in this. Dosage in America is apparently higher than in England, and in both countries the amounts given now are usually

greater than the doses recommended originally, by Wright. It has become the custom in several laboratories to make autogenous vaccines of such strength as to contain 50 million bacteria per c.c., with the exception of staphylococci, which are made to contain 300 million per c.c. The initial dose of such a vaccine is generally $\frac{1}{4}$ to $\frac{1}{2}$ c.c. Subsequent lots of the vaccine may be made stronger if necessary or desirable.

The rule that appears to be very generally followed is that a patient with an acute condition must be given the smallest dose compatible with the severity of the case, while chronic conditions are treated with larger doses. If the dose given is followed by a systemic or local reaction it is probably too large, and the next dose may, with less discomfort to the patient, be smaller. A very slight and transient increase in the severity of symptoms, followed by improvements, is an indication that the dose has been the proper one.

Intervals Between Doses.—The intervals between doses are varied in inverse ratio to the size of the dose and the severity of the disease. The tendency appears to be toward a more frequent administration of very small doses in acute infections. In pneumonia, erysipelas, septicemia, epididymitis, etc., amounts as small as 5 million have been given daily for several days. This plan must still be looked upon as unusual, three days being the more common interval in the acute stage, and five to seven or ten in chronic conditions. At the end of a course of—staphylococcus vaccine, for instance, it is customary to give a very large dose about once a

month to prevent a return of the trouble.

PROPHYLAXIS AND THERAPEUTICS.—The use of bacterial vaccines has already assumed a place of great importance in the prophylaxis of several epidemic diseases, although developments along this line may be said to have barely started. Practical methods have been elaborated for the control of typhoid fever, bubonic plague, and cholera. Although scarlet fever is probably not prevented, it certainly seems to be rendered more mild and its complications less severe by the prophylactic use of a streptococcus vaccine. Much good work has been done in England, chiefly by Allen, upon the prophylaxis of common colds; in this country encouraging observations have been made upon the use of meningococcus vaccine.

At present no sweeping assertions can be made concerning the therapeutic value of bacterial vaccines generally, but the indications are that future progress in the treatment of infectious diseases will be largely along the lines of specific therapeutics. For certain infections, *e.g.*, those caused by the staphylococcus, vaccine inoculation has become the routine method of treatment.

The precise function of the vaccine must be recognized. The parental administration of any foreign protein results in the formation of antibodies. The chief purpose of these antibodies appears to be the removal of their corresponding proteins from the tissues. To accomplish this, it is obvious that direct contact of antibody with antigen is a *sine qua non*. Types of infection in which the bacteria find their focus of growth in

poorly vascularized tissues are therefore the most difficult to influence. Such lesions as hypertrophied tonsils may offer an impassable barrier to the body fluids.

That an accurate bacteriological diagnosis is to be made, and the homologous vaccine used, goes without saying. It appears to be the custom at present when favorable results have not been obtained with a stock vaccine to say immediately, as though there were no other possibility, that an autogenous vaccine is indicated. Possibly it is, but if the dictum should go forth, as would seem to be the desire of some writers, that autogenous vaccines should always be used, the application of bacterial vaccine therapy would be restricted to very narrow limits instead of covering the wide field for which it is destined.

Reports of the therapeutic use of bacterial vaccines must at present be accepted at their face value. Not a few authors seem too enthusiastic, while undoubtedly others are biased the other way. This variation represents so accurately the experience which every physician will have in his practice that it has been thought advisable, in what follows, to give abstracts and quotations from various writers rather than a general summary or expression of personal opinion.

An attempt has been made to bring out in each case the doses that have been used, and the intervals between doses, so that the quotations and abstracts may be of greatest value to the physician who desires to compare his experience with that of others.

TYPHOID FEVER.**PROPHYLACTIC INOCULATION.**

—The universal prevalence of typhoid fever renders it one of the most interesting and important of the infectious diseases from the standpoint of prophylaxis by inoculation. For many years the index of the sanitary conditions in a community has been the incidence of typhoid fever there, and sanitary measures to eliminate infectious diseases have been aimed directly against typhoid fever with the belief that, in general, sanitation which would eliminate the typhoid bacillus as a contamination in food-stuffs, potable water, etc., would go far toward the elimination of every other infectious disease contracted through the alimentary canal. That this belief is well based there can be no doubt, and, even though typhoid vaccination should become more common than it is actually likely to become, public health regulations with regard to the disposal of refuse and the protection of drinking-water, milk, and other foodstuffs must be kept up without regard to specific immunization.

Using the original method of Pasteur, Fränkel and Simonds in 1886 found that repeated, small, non-lethal doses of typhoid bacilli would afford protection to rabbits against fatal doses of the same organism. In the same year, Beumer and Peiper suggested the use of *killed* cultures for the immunization of men, but they made no investigations themselves. Several others reported work on animals, but nothing practical came of it. In 1892, Brieger, Kitasato, and Wassermann proved that it was not necessary to use living organisms,

since killed cultures were equally effective. Up to this time nothing was known concerning the mechanism of typhoid immunity. But in 1893 and 1894 Pfeiffer and others, studying the changes in the bacteria when injected into the peritoneum of a guinea-pig that had been immunized to typhoid, recognized that the degree of immunity depended upon the degree of bacteriolysis. In this study they injected immunized guinea-pigs intraperitoneally with lethal doses of cholera vibrios or of typhoid bacilli. In immunized animals the bacteria were found to lose their motility, swell up, become granular, and finally disappear (Pfeiffer's phenomenon), while in unimmunized susceptible animals the bacteria did not lose any of their motility, increased rapidly in number, and the guinea-pigs died with the peritoneal cavity teeming with germs. It was found later that, if the organisms were mixed with the serum from an immunized animal and the mixture injected into the peritoneal cavity, the same phenomenon took place as when the organisms were injected into the peritoneal cavity of an immune guinea-pig. This demonstrated the possibility of ascertaining the effect of the immunizing process upon an animal. The discovery of agglutinins later by Gruber and Durham and their application to clinical medicine by Widal made the demonstration of immunity easier. Sir A. E. Wright appears to have been the first to inject typhoid bacilli into men, but he did this in the course of an investigation on the coagulability of the blood and not for the purpose of producing immunity to typhoid fever. A few weeks later,

in 1896, Pfeiffer and Kolle immunized two men and investigated the changes in their blood-serum. They were thus the first to actually inoculate men for the purpose of protecting them against typhoid fever. Pfeiffer and Kolle showed that not only were agglutinins produced, but also that the bacteriolytic power of the blood was increased just as during an attack of typhoid fever.

So far as is known at present, artificial inoculation and accidental infection result in the production of identical antibodies. The quantity of bacteriotropic substances seems to be even greater after vaccination than after an attack of the disease, and it is, therefore, not unreasonable to expect the immunity conferred by vaccination to last for a considerable period. This is a question which can only be answered by studies extending over a greater period of time than has been possible since careful observations were started.

In 1897 Wright published the results of antityphoid inoculation upon 18 men, showing that the method was practicable and gave sufficient protection to be worthy of adoption by the army. The next year (1898) Wright introduced prophylactic inoculation into the British Army in India. He used broth cultures which had been incubated for three weeks and which had been killed by heating for one hour at 37° C. The size of the dose was determined by its effect on animals, the quantity necessary to kill a small guinea-pig being used. When the disease became epidemic in South Africa during the Boer War, Wright was given permission by the War Office to attempt to control the

disease by vaccination. Some of the men were inoculated before leaving England, some on the transports, and many more in the field. About 400,000 doses were furnished, and it is believed that 100,000 men were inoculated. No complete returns have been available, although Wright has been able to collect some figures which cover the returns from 19,061 men. He considers that by prophylactic inoculation the incidence of the disease was diminished about one-half and the mortality even more. In spite of this the results were not generally convincing, and many of the medical and line officers were very skeptical of the value of vaccination. In attempting to find a reason for this condition of affairs, it is interesting to note the explanation given by Sir William B. Leishmann, of the Royal Army Medical Corps. The vaccine used during the war in South Africa was prepared under his direction. He states that "the methods then employed in the preparation of the vaccine may have resulted in considerable variations in its vaccinating efficiency. Some men may have received but slight and transient immunity, while others were protected in as high a degree as the system was capable of." It is believed that this variation in the efficiency of the vaccine is possibly due to the method employed for controlling the temperature to which the suspension of bacteria or the bouillon culture was subjected; much of the vaccine was probably overheated. At the present time, Leishmann heats his vaccine to 56° C. for only one hour.

Preparation of the Vaccine.—The preparation of typhoid vaccine does

not differ essentially from the preparation of other ordinary bacterial vaccines. For making it in large quantities, quart bottles known as Blake bottles, or a modification of them, or Roux or Kolle flasks are used. These flasks contain ordinary nutrient agar. The typhoid bacillus is grown on this agar for twenty-four hours. A small quantity of normal saline solution is then run into the flasks, preferably from a Miquel bulb, and the growth is washed from the surface and suspended in this fluid. This thick suspension is collected from the several bottles into sterile Miquel bulbs, both stems of which are then sealed. The bulb is shaken to break up clumps, and a small quantity removed for counting, after which the bulb is again sealed and exposed to a temperature of 60° C. for one-half hour or 55° to 56° C. for one hour. Renaud has reported the use of ultraviolet rays for killing the bacilli by subjecting the suspension to the rays for thirty minutes. After the thick suspension has cooled, it is diluted with normal saline solution and 0.25 per cent. tricresol is added as a preservative. Dilutions are made so that the material for the first dose will contain 500 million killed bacilli per c.c., and for the second and third doses 1000 million per c.c.

The wholesale vaccination of the troops at the front was commenced in February, 1915. Since the beginning of the war the laboratory of the army has sent to the front 5,513,070 doses of vaccine. Between 1911 and the breaking out of the war 20,000 men of the French Army had been vaccinated against typhoid and paratyphoid A and B with mixed or triple vaccine; 200,000 others had been vaccinated against ty-

phoid only, according to H. Vincent (Paris Letter, Jour. Amer. Med. Assoc., Nov. 17, 1917). Thanks to this active immunization, these diseases can be considered as having been practically vanquished. From 6.12 in November, 1914, 7.24 in December, 1914, and 7 in January, 1915, per thousand men, the number of cases dropped to 1.6. In August and September, 1915, the morbidity (paratyphoid predominating) rose to 2.47 and 2.65, but since then it has diminished steadily. During February, 1916, the percentage of cases per thousand was less than 1. In 1917, the rate dropped to 0.063 per thousand. The vaccination by 2 injections is responsible for this remarkable recession in the number of cases and deaths, and the mortality is now so low that one is obliged to evaluate on the basis of 0.3 per 100,000.

Prophylactic typhoid vaccine may be said to be, according to A. Parker Hitchens (Trans. Amer. Therap. Soc.; Med. Record, Aug. 17, 1918), as certain in its value as that against small-pox; it has no serious effects and it becomes now, more than ever, the duty of physicians to demand vaccination of all classes against typhoid fever.

The vaccine is administered by subcutaneous injection. The skin may be scrubbed with soap and water and finally rinsed with alcohol and ether as for an ordinary operation. Practically no untoward results have followed the simpler method of painting the skin with liquor cresolis comp. or iodine. An area about the size of a five-cent piece is painted with tincture of iodine or liquor cresolis comp., and the needle is plunged directly through this painted area. Upon the withdrawal of the needle the excess of liquor cresolis comp. is

wiped away with a piece of clean cotton. Injection of the vaccine intramuscularly possesses no advantage over the subcutaneous method and appears to give rise to more pain and inconvenience.

Local and General Symptoms Following the Injection.—The symptoms following the injection of antityphoid vaccine are similar to those following the injection of other vaccines. The process cannot be considered entirely painless or indifferent, and there should be no attempt on the part of the physician to conceal the fact that there will be some local, and possibly a general, reaction. There is not on record, however, any case of more than a transitory discomfort. For the benefit of those who suffer considerable local pain, it may be remarked that it is believed that, the more severe the local reaction, the higher will be the resulting immunity and also the longer will be its duration.

Fifteen minutes to three hours after the injection, the local reaction commences. It is characterized by some pain and redness, heat, and finally slight swelling of the skin, the area of which may equal that of the palm of the hand. This is somewhat edematous and more or less painful upon pressure, or when the limb is moved. There may be a slight febrile reaction. Following the second inoculation the same train of symptoms may be noticed, but they are more rare and generally less severe when they do occur. The third inoculation is generally accompanied with little discomfort. Among those inoculated in the United States Army there have been found a few very susceptible individuals, but the number of severe reactions has been small, and, regard-

less of their severity, they have disappeared in forty-eight hours.

The condition of the body determining whether the reaction will be severe or moderate is as yet not well understood. There seemed at first to be some evidence that a previous attack of typhoid increased the chance for a severe reaction. It appears, however, that not every patient recovered from typhoid fever has acquired hypersusceptibility to typhoid bacilli, and the severe reaction is not a uniform occurrence in this class of individuals. Those presenting severe reactions who had not had typhoid undoubtedly present the least resistance to the disease when naturally infected.

Only 9 cases from typhoid fever occurred in the army camps of the United States since September 21, 1917, according to George D. Porter (Trans. Amer. Climat. Assoc.; Med. Rec., Sept. 7, 1918). The sick and death rate from this disease was so small as to be considered negligible both in the United States and in Canada.

The men were inoculated in District No. 2 of the Canadian Army between January 1, 1915, and January 1, 1917, 58,382 men 3 times each, making in all 175,146 inoculations. They had had no deaths from these inoculations, and there had been admitted to the hospital for this cause only 117 cases, less than $\frac{1}{4}$ of 1 per cent. of the men inoculated, or about 1 admission to every 1200 inoculations.

Determination of the Efficiency of the Inoculation.—The introduction of the typhoid antigen into the body brings about the production of defensive bacteriotropic substances. These are agglutinins, lysins, amboceptors, and opsonins. The exact practical indication of an estimation of these

various antibodies has been a matter of considerable discussion and investigation. The larger doses of vaccine usually, but not always, give the highest agglutinating, bactericidal, and bacteriolytic titres, and it is believed that the agglutinating power of the serum is of great importance in the valuation of the vaccine. According to Hachtel and Stoner, because of the great variation in individual susceptibility, there is no correspondence between the size of the dose and the amount of the reaction, nor between the severity of the reaction and the amounts of antibodies produced. The French Commission concluded that antibodies are constantly present, though variable in quantity. Pfeiffer, Kolle, Hetsch, and Kutscher have called attention to the lack of constant correlation. Notwithstanding this, the phenomenon of agglutination has become the method of choice for the diagnosis of typhoid fever; although it may not always give an accurate estimate of the value of the vaccine and the degree of the immunity of the person vaccinated, it is by far the easiest to carry out of any of the procedures and gives the practitioner a ready means of checking up the results of his inoculation. Practically everyone has the privilege of submitting specimens of blood to his municipal or State laboratory for the determination of the agglutinin titre.

Concerning the various methods used by the laboratory of the Army Medical School, Russell makes the following statement: "In the course of the last eighteen months we have examined the blood-serum of a large number of vaccinated persons and

have invariably found evidences of immunity. The test for agglutinins is made by the macroscopic method, and the serum dilutions are prepared with great care. The increase in the agglutinins is evident by the sixth or seventh day, and the rise in opsonins follows quickly. The Widal is positive in high dilutions of the serum, in many cases being present in a dilution of 1 in 5000 to 10,000 or even 1 in 20,000. Only rarely does it fail to rise above 1 in 500 or 600. It reaches its maximum soon after the third dose and falls rapidly at first and then more slowly toward normal. In a few of the cases examined it is found to have reached normal within a period of six months, but oftener has remained present for nearly a year. In the two charts exhibited the Widal is still present after seventeen and twenty months. These charts also show the curves of opsonins. We do not use the opsonic index of Wright, but make serum dilutions just as for the agglutination reaction. To a portion of the serum of each dilution is added a definite quantity of bacterial emulsion and a few drops of a suspension of guinea-pig leucocytes according to the method of Neufeld. After incubation, spreads are made from each tube, and the titre or phagocytic power of the serum is established by observing which serum dilutions cause greater phagocytosis than is found in the normal serum controls. This method has given regular and consistent results, and we find the opsonic power of a serum to be just as definite a thing as its agglutinating power. In recovery from typhoid fever it is not at all improbable that the opsonins are

more important than any other of the known antibodies. The opsonic curve is never as high as the curve of agglutins, nor does it continue above normal as long.

"Our bacteriolytic tests have been made *in vitro* according to the method of Stern and Korte, but, as occasional erratic determinations occur, the curves have not been charted. No determination of bacteriolytic amboceptors by means of Pfeiffer's experiment has been made.

"The leucocyte count is temporarily, but regularly, raised after each dose of vaccine. The rise is often to 15,000, but it soon begins to decline and reaches normal in about ten days."

Practical Results of Typhoid Inoculation for Prophylaxis.—The literature which has accumulated during the past few years concerning the prophylactic value of typhoid vaccine is voluminous and overwhelming in establishing the efficiency of this measure from a practical standpoint. They have placed the value of typhoid vaccine beyond question.

The *length of the period* of complete protection is generally admitted to be about one year, though a certain partial protection may last much longer.

Typhoid vaccination is now compulsory in the American Army. General Orders No. 76, War Department, Washington, June 9, 1911, required all recruits under 35 years of age to receive antityphoid vaccine as a prophylactic measure. This was followed by General Orders No. 134, September 30, 1911, to include all officers and enlisted men under 45. In addition to this, during the past year

many hospitals have required all internes, nurses, and other attaches of such institutions, especially those coming in contact with patients, to be protected against typhoid fever by inoculation. The Samaritan Hospital was the first in Philadelphia to establish this rule.

Lieutenant Foster (Jour. Amer. Med. Assoc., vol. lv, pp. 1808-1809, Nov. 19, 1910) says: "Laboratory researches demonstrate that the agglutinin, opsonin, and bacteriolysin of the blood-serum are increased by antityphoid vaccination, and that the increase is greater and more persistent than that conferred by an attack of typhoid fever. Typhoid outbreaks in commands in which there were both inoculated and uninoculated individuals have demonstrated, practically, what we should have expected from the laboratory evidence.

The serum gives a positive agglutination reaction in every one who has been vaccinated against typhoid, according to M. Ascoli (Riforma Medica, June 12, 1915). The diazo and chromogen reactions, the leukopeny and aneosinophilia are also the same in the typhoid patient and in those merely vaccinated against typhoid. There is a difference, however, in that agglutination occurs at a greater dilution in true typhoid so that a quantitative sero-diagnosis is still possible. The agglutination response varies also differently with true typhoid when the test is repeated. Cultivation of typhoid bacilli from the blood and bile (after ingestion of oil) and the hemolysis test are the main reliance now to differentiate typhoid patients and detect carriers. If the bile is added to bouillon containing

serum known to agglutinate typhoid bacilli, if typhoid bacilli are present in the bile they will be agglutinated in clumps in six hours.

The duration of immunity after inoculation for typhoid is uncertain. Immune substances can be found in the blood for a varying time, sometimes for several years, and after they have disappeared, the individual responds more quickly to another inoculation. According to Alexander Fleming, (*Practitioner*, January, 1916), it has been observed in the British army in India that while in the preinoculation days the most dangerous period, as regards typhoid, was the first year of the soldier's sojourn, the maximum incidence now is in the third year. This seems to show that the immunity conferred by the vaccine lasted at least 2 years.

President Taft, in an address before the Medical Club of Philadelphia, May 4, 1911, speaking of sanitary achievements and the immunizing value of typhoid vaccine during the present mobilization of troops on the Mexican border, said: "The percentage of typhoid cases (in the Spanish-American War) was so high that it is hard to believe that of 120,000 men there were 20,000 cases, with a case-mortality of 7 per cent. Of the volunteer regiments mobilized during the Spanish-American War, 90 per cent. became infected with typhoid fever within eight weeks from the date of mobilization. Today, two months after mobilization, with the modern health regulations and by the use of vaccination against typhoid, not one case of typhoid fever has appeared in the entire force, except that of one teamster, who was not vaccinated. It is hard to credit the accuracy of such

a record. But, as I have it directly from the war office, I can assert it as one more instance of the marvelous efficacy of recent medical discoveries and practice."

After reviewing statistics of wars and results of antityphoid vaccination in the British Army under Wright and Leishmann, Major Russell (*Johns Hopkins Med. Bulletin*, vol. xxi, pp. 83-91, Mar., 1910) proceeds to discuss the results of its use in the United States Army. When the report was made 1400 complete vaccination records had been obtained. He states that each dose of vaccine is followed by a local reaction, which varies very little either with the size of the dose or with the idiosyncrasy of the individual. As a rule, there is a red, tender spot about as large as the palm of the hand at the point of injection, making its appearance six or seven hours after injection and reaching its full development in about twelve hours. After this it gradually disappears and has entirely subsided in forty-eight to seventy-two hours. Occasionally the local reaction is somewhat more severe; the lymph-glands may become slightly swollen and tender to pressure; however, local applications have never been necessary, and in no case has suppuration developed. The general reaction varies in its symptoms. In children and in many adults it can be said to be absent. In its milder form it causes a transitory headache and a feeling of malaise which lasts from two or three hours to a day. Slightly more marked general reactions are evidenced by considerable headache and a decided feeling of lassitude. Occasionally there are chilly sensa-

tions without much rise of temperature. A few have complained of nausea and a very few of diarrhea lasting a day. The men described their condition as "I thought I was going to have a cold," "a sore throat," or "an attack of grippe." Moderate reaction is characterized by a rise of temperature to 101° to 103° F. A few have had bad chills. Severe reactions are those showing temperature 103° F. and more. They complain of chills, more or less headache, nausea, vomiting, or herpes labialis; no case of albuminuria has been reported.

The following table gives a graphic representation of the effects of vaccination according to age:—

THE PERCENTAGE OF DIFFERENT REACTIONS AT VARYING AGES.

Age.	First dose.				Second dose.				Third dose.				
	Absent.	Slight.	Mod.	Severe.	Absent.	Slight.	Mod.	Severe.	Absent.	Slight.	Mod.	Severe.	
0 to 10	73	20	06	00	100	00	00	00	93	07	00	0	0 to 10— 15 cases
10 to 20	80	14	04	01	81	16	01	00	94	03	02	0	10 to 20— 97 "
20 to 30	61	31	06	01	71	22	04	01	81	15	03	1	20 to 30— 595 "
30 to 40	50	39	09	01	62	26	08	01	73	22	02	1	30 to 40— 153 "
40 to 50	42	46	08	01	66	26	07	03	70	29	00	0	40 to 50— 24 "
50 to 60	33	60	06	00	46	03	00	00	54	45	00	0	50 to 60— 5 "
													880 "

In reviewing the history of typhoid vaccination, Russell thinks the opinions of the following men are perhaps in part responsible for its slow adoption:—

Wright, fearing the results of a negative phase, advises the use of two weaker injections instead of one large and efficient one, which, in other words, means "a long-range prophylaxis."

Flemings, of the German Army, reports severe local reaction and

marked prostration. The vaccine he used was prepared according to Pfeiffer and Kolle, and is about four times as strong as ours. Dosage was formerly largely based on animal experimentation, and, as many laboratory animals not susceptible to the disease are relatively resistant to the endotoxins, excessive amounts were used. Now, we have record of many thousand vaccinations of human beings, and a great deal of the reaction trouble due to large doses has been eliminated. The greatest objection with which we have to contend is the very prevalent idea of the *negative phase*. This we owe largely to Sir A. E. Wright. He quotes Ehrlich and Madsen, but reference to their papers

will show that they were not dealing with a first dose, but with the effect of a dose of toxin on an animal already immunized. Ehrlich's and Madsen's studies were mostly made with diphtheria and tetanus toxin and not with typhoid. Typhoid does not produce exotoxin. In Wright's work it appears that he did not obtain a decrease of the quantity of antibodies below the normal, but merely somewhat below the level obtained during a preceding immunization. Careful

study of Wright's work shows that in his opinion the negative phase² is not necessarily associated with every immunization process, but is due to avoidable causes, *e.g.*, excessive dosage.

Pfeiffer and Friedenberger have been interested in this question, and Emery summarizes their work as follows:—

"They conclude that the fear of a negative phase is exaggerated, and it must not be forgotten that the essence of the 'opsonic therapy' consists in administering a dose of vaccine, in the first instance, while the index is low. There is thus no direct proof that the period of the negative phase is coincident with the period of hypersensitiveness to infection. And when we compare it with the period of increased sensitiveness to toxins we find that, whereas the negative phase comes on almost immediately, the hypersensitiveness to toxins or tuberculin or anaphylaxis to serum takes some days to develop."

Col. Leishmann (personal communication to Russell) says that the negative phase in typhoid vaccination is a negligible factor.

In his summary Russell says that vaccination against typhoid is undoubtedly protective; that it is indispensable in the army; that *there is no increased susceptibility immediately following inoculation*; that the statement that *vaccination should not be undertaken during epidemics is not justified by the facts at hand*, and that untoward results have not occurred in his series of 3640 vaccinations.

In answer to the question: Should antityphoid vaccination be done during an epidemic of typhoid fever, Heger

and Mockel (Münch. med. Woch., June 25, 1918) relate an epidemic of typhoid which occurred in the insane hospital at Wiesloch of which they vaccinated all the inmates and personnel (1500 persons in all). The percentage of rise in temperature above 101.5° F. was 2.5—2—1.5 per cent. for the first, second, and third injection respectively. Of these 129 cases of typhoid that occurred, the proportion of serious cases before vaccination was 44 per cent. and 23 per cent. among vaccinated subjects. Eight subjects were vaccinated during the incubation of their typhoid, the disease running a normal course with, perhaps, a lower temperature than usual. No complications were observed and the epidemic was, in fact, nipped in the bud. Therefore the writers reply in the affirmative to the question submitted.

On the whole, the recent great war has abundantly emphasized the value of protective vaccinations.

In the entire army of over 90,000 men prior to the war, according to Russell (Jour. Amer. Med. Assoc., lxii, 1371, 1914), only 3 cases of typhoid fever, with no fatalities, occurred during the year 1913. It has been claimed that antityphoid inoculation renders the recipient more susceptible to tuberculosis or tends to activate latent tuberculous foci. Tuberculosis in the army not only has not increased since the introduction of vaccination, but it has actually decreased. The conclusion is inevitable that the prophylactic vaccine as used in the army has given almost absolute protection against typhoid fever without producing untoward effects of any character.

Of the first Canadian expeditionary force, when it was at Valcartier, P. Q., 27,000 men received antityphoid inoculation, involving 57,000 injections, ac-

cording to Captain Harry Morell (*Brit. Med. Jour.*, Feb. 13, 1915). No cases of severe constitutional reaction, nor any infected arms followed the injections. The primary dose of the serum was made up so that 1 c.c. represented 500 million killed bacilli; the secondary dose contained 1 billion. The Record syringe, of 10 c.c. capacity, was used so that 1 syringeful furnished 10 men. The usual site of injection was the deltoid region; the skin was first painted over with 10 per cent. tincture of iodine. An injection consumed about 17 seconds and 2 operators could easily inoculate 1000 men in 1 morning. After the needle was withdrawn, it was wiped with absorbent cotton impregnated with alcohol and then flamed in a lamp.

Yagisawa (*Paris méd.*, May 27, 1916) states that during the period between the war with China and the war with Russia (1897 to 1903), the morbidity averaged 5 per thousand of the average force of 125,629 Japanese troops, with a mortality of 1 per thousand. Then the morbidity increased to 8 and the mortality to 1.3 per thousand. Antityphoid vaccination was then introduced, in 1908, and the morbidity dropped to 0.7 and the mortality to 0.08 per thousand among those vaccinated more than once while the figures remained at the same height among the non-vaccinated and the civilian population. Other tables compare the course of the disease in the 412 vaccinated who developed it and in the 2533 non-vaccinated, showing the comparative mildness in the former. One table lists the interval between the vaccinations and the onset of the disease. In 69 the interval approached or surpassed one year. Intestinal hemorrhage occurred in only 6 per cent. of the 266 vaccinated typhoid patients and

in 16.4 per cent. of the 122 non-vaccinated.

Chantemesse (*Bull. de l'Acad. de Méd.*, Aug. 29, 1916) points out that there were only 136 cases with 7 per cent. mortality among the 80,000 men who were vaccinated, while there were 525 cases with mortality of 14 per cent. among 60,000 not vaccinated. The figures include both typhoid and paratyphoid. Only one fatal case of typhoid occurred in a man who had been completely vaccinated, and in this case staphylococci were isolated from the meninges. Three of the fatalities were from paratyphoid.

Typhoid in the vaccinated has been the subject of much comment, but the summary of this phase of the problem given by Carnot and Weill-Halle (*Presse Méd.*, Mar. 18, 1915) exemplifies accurately the teachings of clinical experience garnered during the war:—

In an immense majority of cases, preventive inoculation confers complete immunity; in certain rare cases, those vaccinated have a light fever of typhoid type; bacteriological examination shows in these cases a paratyphoid organism, but oftener the typical bacillus; insufficient immunization may occasionally be attributed to defective methods of vaccination; the feebleness of immunity is connected sometimes with bodily weakness from overwork; sometimes feeble immunity depends on the number and strength of the infecting bacilli; even if immunization is not perfectly satisfactory, it will generally be noted that fever in those inoculated is benign, short in duration, and without complications.

Stefansky (*Russky Vrach*, xvi, No. 3, 1917) observed that on an average 1 out of every 400 or 500 men vaccinated against typhoid showed considerable

disturbance. The temperature ran up to 102 or 104, with vomiting, diarrhea, jaundice, transient albuminuria and syncope. The symptoms disappeared within a couple of days.

Typhoid Fever after Prophylactic Inoculation.—A number of cases of typhoid fever were reported by C. P. Brown, F. W. Palfrey, and L. Hart (Jour. Amer. Med. Assoc., Feb. 15, 1919), which began to appear about the end of June, 1918, among troops stationed at Camp Greene, N. C. Of the cases reported 12 had previously received the full dosage of antityphoid vaccine, 2 recruits had each received 2 doses of vaccine, 2 had received a single dose each, and 2 had not been inoculated. A mild epidemic of typhoid occurred concurrently in Charlotte, the nearest city to the camp, and infection was thought by the health authorities to be fly-borne. As this mode of infection was not considered probable in the camp, careful investigations were made in regard to the milk, water, and ice used, but no particular information was elicited. Cultural examinations were made of the blood, urine, and feces of the 18 cases reported; the blood was positive in 13 cases, or 72.2 per cent.; the urine in the same number of cases, and the feces in 9, or 50 per cent. Cross agglutination tests showed wide variation, both as regards individual strains and the preparation of the agglutinating fluid by different methods, thus demonstrating the desirability of using standard agglutinating fluid for Widal tests. The results of these tests also strongly suggest that the same method should be used in checking the agglutination of patients' serum with the homologous strain. The authors conclude

from their observations on these cases that occasional cases occur in which the usual preventive inoculations against typhoid fever fail to protect against the disease, most probably on account of the ingestion of virulent organisms in massive doses. They suggest the following precautions as a means of prevention: (1) Care should be taken that cooks and food handlers are not changed and new ones put in their places without examination for carriers of *B. typhosus*. (2) Special inquiry should be made by the surgeon of all prospective cooks and food handlers with reference to their having had typhoid fever, and note of this made when specimens are submitted for examination. (3) Repeated examinations should be made of prospective food handlers whose history is suggestive of typhoid fever before the men are accepted for such work. (4) Clinical cases of typhoid fever should have intensive study made of both urine and feces.

Therapeutic Value.—Much work has been done at various periods with regard to the specific therapy of typhoid fever. Among the first was Fraenkel. Chantemesse also attacked the problem from another standpoint, using a serum. The results obtained by Chantemesse have been unique. No other person has been able to obtain results comparable to those reported by him, and a careful perusal of the papers published by Chantemesse makes one wonder whether some error had not modified the figures intended for publication. A few years ago various substances were used for the treatment of typhoid fever by M. Wymann Richardson at the Massachusetts General Hospital. Richardson concluded from the use of vac-

cines, split products (Vaughan), and serums that these methods of treatment did not reduce the mortality; they did not shorten the course of the disease, but relapses were apparently less frequent, and some of the patients were probably more comfortable than if they had not received such treatment.

Occasionally the treatment of the disease by bacterial vaccines, and serums as well, is attended by brilliant results.

MacGillcuddy (Lancet, Sept. 25, 1915) observed that the treatment of typhoid fever with vaccines reduced the severity of the disease in many cases, but that in these there was a greatly increased tendency toward relapse. He agrees with all observers that these relapses are usually mild, seldom fatal, and of little serious moment.

Results obtained in military practice in Serbia with vaccine treatment in typhoid fever have been reported by Petrovitch (Bull. de l'Acad. de méd., June 13, 1916). Whereas, among 1020 cases treated by ordinary measures the mortality was 12.8 per cent., among 2270 other cases subjected to vaccine treatment, without the administration of cold baths, it was only 2.7 per cent. Small doses—5 to 50 millions of typhoid bacilli killed by heat—proved as efficacious as larger ones. Where results were slow in appearing, and in complicated cases, the dose was reduced rather than augmented, and such reduction proved essential for benefit in these patients. Very toxic cases, often in subjects greatly exhausted and already weakened by dysentery or cholera, proved in no way refractory to the treatment except when the eliminatory functions were impaired. A few of these patients, however, died in conva-

lescence, rather from extreme cachexia and anorexia than from myocarditis. In cases with renal or myocardial complications, and in general when elimination is in abeyance, the writer counsels great reduction in the dose, lest uncertain or even unfavorable results ensue. The dose in general should be based, first, on the rule that all pronounced local and general reactions are to be avoided, and second, on the general progress of the case, in particular the temperature, with due attention to the functions of the liver, kidneys, skin, respiratory apparatus, and intestine. Small doses are of advantage in avoiding excessive excitation of the tissues as well as an excessive production of antibodies, with resulting massive liberation of endotoxins and stress on the eliminatory organs. Sometimes the pulse became soft when the temperature dropped and the general condition improved. This peculiarity was noted at times after the first vaccine injection, but especially after the second or third, the patient, however, presenting no other manifestation of cardiovascular disturbance. The habit was accordingly formed of giving a little **caffeine** internally after the second injection. This always improved the pulse and counteracted the weakness previously noticed.

Anders (Jour. Amer. Med. Assoc., vol. 1v, 24, Dec. 10, 1910) treated 8 typhoid-fever patients with small doses of typhoid vaccine. The initial doses were 20 million and the subsequent ones 50 million each. These were repeated at intervals of seventy-two hours as a rule. It is the belief of Anders that large doses should not be used because there may be danger of increasing the toxemia. In this series of 8 cases in all save 1 of which

the Widal reaction was present, no reactionary fever occurred, but in two instances the nocturnal remissions became distinctly greater immediately after the use of the vaccines and in one instance of protracted subfebrile temperature. It would seem that the injections were sufficiently powerful to cause a gradual decline of temperature to normal in the course of several days. In 1 case a relapse occurred. Anders believes that, while the routine use of typhoid vaccine is not to be encouraged, it should receive a more extended trial than hitherto, particularly in the **earlier stages** of mild types of the disease, before it is finally rejected. It certainly has a place in the prophylaxis of typhoid fever: in suitable cases when continued during convalescence, to prevent relapse; to combat local infections with the typhoid bacillus, as, for example, bone suppurations which arise in the period of convalescence, and for the removal of the typhoid bacilli from the feces and urine in the case of typhoid carriers.

Callison has been using an initial dosage of 500 million, repeating the injections at intervals of four days and increasing the dose 100 million at each subsequent injection. He has collected statistics of 323 cases of typhoid fever treated with vaccines. These showed a mortality of 5.2 per cent. This certainly compares favorably with the 16 per cent. reported by Bellevue and allied hospitals.

On the other hand, a careful comparison between cases treated by usual methods and an equal number treated by vaccination does not seem to have shown that the latter merited greater confidence than the former under similar conditions of nursing, food, etc.

Out of 230 cases studied by T. H. Whittington (*Lancet*, Apr. 8, 1916), 115 were vaccinated and an equal number were held as controls. In the total vaccinated cases there were 29 in which it appeared that vaccine had a definite good influence. Of these, 20 belonged to those classes in which the prognosis is good. Among the cases in which the vaccine appeared to do good none had severe lung involvement. Those cases which had much bronchitis or bronchopneumonia (the average severe case) ran the severe course which is usual and vaccine appeared to be of no avail. On the whole, it would seem (*a*) that it is in just those cases in which the physician so much requires help that vaccine is disappointing; (*b*) that vaccine neither shortens the fever nor reduces the number of complications in even that class of case which is likely to do well; and (*c*) that there is a decided suspicion that vaccine increases the incidence of hemorrhage.

Bacillus Carriers.—Several workers have described successful results obtained from the use of vaccines in the treatment of typhoid carriers. Such treatment seems to rid the system of the organisms and to improve the general condition of the patient. Dr. Randle Rosenberger (*N. Y. Med. Jour.*, Mar. 26, 1910) has reviewed the literature concerning carriers up to the time of the publication of his paper.

Irwin and Houston (*Lancet*, 1, p. 311, 1909) report the case of a typhoid-bacillus carrier treated with vaccine. The typhoid bacillus was found in the urine, but not in the feces. The blood gave a typical Widal reaction. The initial dose of 50 million bacilli caused a rise in temperature for a few days, together

with considerable malaise and headache. A week later the injection of 100 million was followed by less marked disturbance than after the first injection. The urine was examined as before, and the colonies which developed on the Petri plates were much fewer than on previous occasions. Two weeks later 200 million were injected. The urine examined after this inoculation showed as many typhoid germs as before. The patient was put on sodium lactate to make the urine alkaline, and three weeks later an injection of 300 million was given. No typhoid bacilli could be found in the urine after this injection. Two weeks later an injection of 500 million was given, and four weeks afterward 1000 million were injected. No bacilli could be found in the urine or feces. The Widal reaction was still marked. The patient had increased markedly in weight, and her general condition had returned to normal. The apparent success of the vaccination treatment in the case recorded encourages the authors to think that vaccine therapy may furnish us with an effective means of dealing with these dangerous carriers of infection. It is interesting to note that the production of an alkaline reaction in the urine aided the blood to clear the urinary tract of bacilli. It is frequently observed in cases of pyelitis that the temperature falls whenever the urine is made alkaline by such drugs as citrate of potassium and lactate of sodium. This is probably due to the fact that the acidity of the urine bathing the mucous membrane of the urinary tract interferes with the action of the phagocytes.

Goubau (*Arch. Med. Belges*, July, 1917) studied this question in 30 convalescent carriers treated with autovaccine or a Wright monovalent vaccine, in weekly injections. The bacilli disappeared completely in 2 months in all of the 23 thus treated during the first 5 months after the disease. They apparently establish the efficacy of this autovaccine method of curing carriers. The bacilli disappeared from the convalescents given the vaccine treatment much earlier than in those not thus treated. The effect was prompter the shorter the period after defervescence when the autovaccine was commenced. After an interval of 5 months no appreciable effect was apparent in 43 per cent. of the cases. When the interval had been only 2 months, 6 carriers were cured with 3 injections; 3 with 4 and 2 others with 5 and 6. The precautions are those for vaccine therapy in general. One case warns to be on the alert for latent tuberculosis as there is a possibility that the repeated vaccine injections may have contributed to the development of frank tuberculosis soon after.

The writer also studied the persistence of bacilli in 431 persons of all ages and both sexes who had been vaccinated once against typhoid and 246 unvaccinated. Of this total 677, 14.33 per cent. still harbored typhoid, but the vaccinated got rid of them sooner than the non-vaccinated, although the difference is not marked. None of the vaccinated were carriers of typhoid bacilli beyond the seventh month, while they were found up to the sixteenth month in 0.43 per cent. of the unvaccinated. No carriers of paratyphoid A were found after the fifth month or of B after the seventh.

Clements and Dawson report the

treatment of a chronic typhoid carrier by a specific vaccine. This man received six injections of vaccine, starting with 125 million and increasing up to 600 million, over a period of four months. An attack of cholecystitis developed, but disappeared without other treatment. Although the last attack of hepatic colic occurred one month after the last injection, typhoid bacilli could no longer be isolated from the feces. The writers believe the case is interesting as being the first recorded cure of a gall-bladder carrier. As to whether the treatment by vaccine was the cause of the attack of cholecystitis they are unable to give a definite opinion. It is, however, certain that the cholecystitis was the immediate cause of freeing the gall-bladder of all foci of the infection.

Brem and Watson (Arch. Int. Med., vol. viii, pp. 630-638, 1911) have carefully reviewed the literature of the past five years concerning reports of chronic typhoid-bacillus carriers. There has been little discussion of the treatment of these patients, probably because treatment has been unsatisfactory and in but few cases has the infection been eradicated. These writers report the successful treatment of one case with autogenous vaccine.

Their summary is as follows:—

"1. The literature of the treatment of typhoid-bacillus carriers is reviewed. Eleven recoveries, excluding our case, have occurred. Five of these patients recovered during vaccination with autogenous vaccines.

"2. Our patient was a white child, female, aged 4½ years. Shortly after her attack of typhoid fever her father and mother were infected. Typhoid organisms in pure culture were iso-

lated from the child's urine. Hexamethylenamine had been administered to the patient during two weeks of convalescence from the typhoid attack.

"3. Practically the only treatment given was vaccination with autogenous vaccines. Nine doses were given, increasing from 25 to 1500 million. The bacilli decreased gradually, and disappeared after the ninth vaccination. Eleven successive urine cultures were positive for *B. typhosus* and then five successive cultures were negative.

"4. The total duration of the bacilluria, from the time of normal temperature, was about six months. The patient appeared to be a continuous carrier.

"5. It seems that the disappearance of the bacilli was not an intermission but a true recovery, brought about by the gradual healing of a chronic lesion under the influence of vaccination."

In an ophthalmologic service where 22,000 troops were vaccinated against typhoid, Bussy (Lyon Méd., Jan., 1919) saw 5 men who developed ocular lesions thereafter. Two of the men had kidney disease, but it was latent and difficult to detect. After the vaccination, 1 developed albuminuric retinitis and died of uremia 2 months later. He was a man of 45. This suggests the advisability of testing the blood-pressure as well as examining the urine before vaccinating against typhoid. The other patient presented severe hemorrhages in both retinas after the typhoid vaccination. The 3 other men developed herpes and ulceration of the cornea, but recovered without impairment of vision.

Paratyphoid Bacilli.—Two of the most important and most interesting organisms similar in many characteristics to the typhoid and colon bacilli are the paratyphoid bacilli. There are two of these—paratyphoid A and paratyphoid B. Paratyphoid B is more closely related in its cultural characteristics to the typhoid bacillus, while paratyphoid A stands closer to the colon bacillus. Both are mildly pathogenic and may cause a condition clinically identical with typhoid fever. The symptoms are not often severe, and the death rate is low. The diagnosis may be made by blood-culture or by the agglutinin reaction. Of conditions diagnosed as typhoid fever, from 3 to 10 per cent., according to the locality, are in reality caused by one of the paratyphoid bacilli. When the agglutinin reaction is persistently negative with typhoid bacilli and the clinical diagnosis is typhoid it is advisable to try the agglutinin reaction with typical paratyphoid cultures. The fact that paratyphoid infections have not been recognized more commonly is due to failure to carry out this procedure.

Although paratyphoid B infections are more common, the A type has also caused epidemics. Both have caused epidemics of food poisoning.

In view of the prevalence of infection due to the paratyphoid bacilli a prophylactic vaccine containing both the typhoid and the paratyphoid bacilli is indicated. It has been found repeatedly that immunity to typhoid fever has no influence upon the susceptibility of the individual to infection with the paratyphoid bacilli.

Widal and Salimbeni (*Presse méd.*, Jan. 4, 1917) employ a simple emulsion of typhoid and paratyphoid A and B

bacilli killed by heat in 9:1000 saline. It contains 10 billion germs to each 3 c.c. This is injected, first .1 c.c. and then 2 c.c. after a 7-day interval. Nearly 5000 persons thus vaccinated showed no more reaction than with the weaker vaccines, while the antibodies in the blood were later found as abundant as in those given the usual 4 doses.

Isolation and Identification of Typhoid Bacilli.—Various laboratories have developed their own methods for isolating typhoid bacilli from blood, feces, and urine, but the general principles at the base of them all are the same. If the specimen is blood, some enriching method is used; if feces, the material must first be diluted in sterile broth or salt solution. Such a dilution of feces or urine may first be inoculated into an enriching medium, as broth or bile medium, and incubated, or it may be immediately streaked upon a differential medium, such as the Conradi-Drigalski or the Endo medium. Characteristic colonies are fished after twenty-four hours and final diagnosis made, including agglutination tests with a specific immune serum of high titre.

The modified Endo medium devised by Kendall and Day (*Jour. Med. Res.*, Sept., 1911) has much to commend it. It contains 15 grams of agar per liter, instead of 40, which results in the development, after eighteen hours, of larger and more distinct colonies than appear in 40-gram agar. The second point of divergence from the original is in the reaction, which is made just alkaline to litmus instead of being strongly alkaline to it, so that those bacteria forming acid have less alkali to neutralize and show their characteristic changes very quickly.

., F. F. Russel (Jour. Med. Res., vol. xxx, pp. 217-229, Sept., 1911) has proposed a new double sugar tube medium, the use of which he interposes as a step between the use of a modified Endo medium and the agglutination test. Typhoid-like colonies fished from Endo streaked plates are inoculated upon these tubes, on which the reactions of typhoid, paratyphoid, dysentery, and coli are very distinctive. Growth upon tubes showing characteristic typhoid reaction can be used for macroscopic agglutination test. One great advantage derived from the use of this medium is the elimination of a great bulk of the work involved in testing for agglutination, all typhoid-like colonies appearing upon the Endo plates.

The medium proposed by Russel is a litmus agar containing glucose and lactose (the composition is given later). It is slanted and inoculated by a combined streak and stab. As described by Russel, "The entire point of the medium rests upon the difference in the changes produced by the growth of the typhoid bacillus under aerobic and under the imperfect anaerobic conditions found in the butt of the tube, where the bacillus obtains its oxygen by breaking down the glucose with the liberation of considerable acid; on the surface, however, in the presence of free oxygen, no acid is formed."

The characteristic appearances of the various organisms commonly isolated from feces are as follows:—

Typhoid bacillus: on the surface, a filiform, colorless growth on a blue background; the upper part of the tube is unchanged in color, but the lower part, the butt, is a brilliant red.

Colon bacillus: growth accompanied by a large amount of acidity and gas.

Alkali formers: no change in the medium, or slight increase in blueness.

Staphylococcus: reddening only in upper part of tube.

Streptococcus intestinalis: beaded growth, with slight reddening throughout the tube.

B. subtilis: heavy, rough surface growth, usually leaving medium unchanged; though it may possibly be reddened below with no gas formation.

B. pyocyaneus: greenish-blue surface growth, color of medium being unchanged.

B. proteus: small gas bubbles in depth, reddening and then decolorizing the butt very early, the upper part of the tube being unchanged except for the spreading surface growth.

All *dysentery bacilli* produce reactions similar to that of typhoid except that the quantity of acid is less and reddening occurs usually only along the line of the stab.

Paratyphoids (no distinguishing characteristic mentioned by Russell for differentiation of A and B types): upper part of medium unchanged, surface growth like typhoid, slight amount of gas as well as reddening in the butt.

Slow *colons* simulating *paratyphoids* may be eliminated by agglutination tests.

Emphasis should be laid upon the fact that all readings of reactions in this medium should be made early. Russel gives eight to eighteen hours as the period of characteristic reaction. After twenty-four hours there may be change in appearance due to

spread of the growth or diffusion of the acid or alkali formed. This is particularly noticeable in the case of typhoid cultures. If the medium has been freshly slanted so that it is still moist when inoculated, the surface growth becomes heavy and spreading with a consequent production of a large amount of alkalinity. After several days this may spread downward into the medium.

The double sugar medium is prepared as follows:—

Enough 5 per cent. aqueous solution of litmus (3 to 5) is added to plain agar (2 or 3 per cent.), which usually has a reaction of about 0.8 per cent. acid to phenolphthalein, to give it a distinct purple-violet color, the amount of litmus depending on the original color of the agar, dark requiring more than light, and the reaction is then adjusted by adding sodium hydrate until the mixture is neutral to litmus. Next, and last, 1 per cent. of lactose and 0.1 per cent. of glucose dissolved in a small amount of hot water are added and the medium tubed for slants. The sterilization is done in the Arnold, and because of the danger of breaking down the lactose must not be carried too far; if the tubes are packed loosely in the sterilizer basket and allowed good circulation of the steam, ten minutes on the first and fifteen on the second day have been time enough. The tubes are then slanted and stored in small quantities in a dark place.

Mixed Infections in Typhoid Fever.

—The results from the use of typhoid vaccine in practically all the armies of the civilized world are well known. These results are in such marked contrast to those obtained in treat-

ment with the vaccine that an interesting problem is presented. The problem is made particularly interesting from the fact that the treatment is occasionally attended with brilliant results. There is, however, apparently no uniformity in this, and up to the present no one has been able to make any prediction as to whether a certain case might respond to the vaccine or not. In seeking an explanation the pathogenesis of the disease must first be considered. There is now no doubt that the *Bacillus typhi* of Eberth is the cause of typhoid fever and that it gains entrance to the body through the alimentary canal. The period of incubation is generally given as from five to twelve days. The chief site of the local lesion is in Peyer's patches of the intestine. These begin to swell on about the ninth day and finally, at the beginning of the third week, break down to form ulcers. Up to about this time there is a bacteremia; the bacilli have been isolated from the blood early in the disease by numerous persons. But as the disease progresses cultures from the blood become more difficult to obtain. With the development of the rose spots the organisms apparently disappear from the blood.

One of the most important phases of this subject is the period of disease at which patients generally enter hospitals. It is safe to say that 75 per cent. do not enter before the beginning of the third week, and at the time when ulcers have developed or are about to develop in the intestine. The bacilli have disappeared from the blood and the condition of the patient is no longer due solely to

infection with the typhoid bacillus. The pyogenic and possibly some of the saprophytic bacteria present in the intestine find a suitable culture medium in and about the ulcers, so that at this time the typhoid bacillus is only one of the several factors continuing the infectious process. For the successful and consistent specific therapy of the disease, then, it will be necessary to ascertain what organisms are responsible for the mixed infection and to use a vaccine containing these bacteria.

This is not an easy task. Blood-cultures are of no avail because at this period the blood is generally sterile. Occasionally the typhoid bacillus may be isolated from the urine, but the true secondary infecting bacteria may never find their way into the urine. It is probable that the organisms in question are represented in the feces, but there must be many others which take no part in the infection and some of those desired may be killed off by the time the bowel contents are evacuated. To collect and select the proper ones from this source is likewise attended with difficulty. Some work has been projected in which the organisms isolated from the feces will be checked up against complement-fixing and agglutinating substances in the blood-serum. It is hoped in this way that some idea of the organisms taking a prominent part in the infection, at least those which cause antibodies to be deposited in the blood-stream, may be recognized.

If this method fails the suggestion does not seem irrational to isolate from typhoid feces representative types of well-known pyogenic bac-

teria, and to test these out therapeutically—in such small doses, of course, that no harm will be done the patient even if no benefit accrues.

It is also proposed to obtain typhoid ulcers at autopsy as quickly as possible after death or at operation, and after rinsing in sterile saline solution to remove the excess of foreign matter, and study the bacterial flora of the surface and of the deeper parts of the ulcer. This method should give more direct results, but the difficulty of obtaining ulcers that have not undergone post-mortem changes is so great that such work is likely to be seriously hampered.

Typhoid fever is in reality a mixed infection; the chief function of the typhoid bacillus is exercised in preparing certain tissues for various other organisms, and for this reason the specific therapeutics of the disease by typhoid vaccine alone is of limited value. Those patients in whom positive results have been obtained with it are in all probability cases in which there has been very slight or no ulceration of the intestine. Not everything, however, may be attributed to the bacteria. It must not be forgotten that the absorption of intestinal products plays an important part in the development of the clinical picture; the long-continued pyrexia certainly is not without effect upon the tissues.

Furthermore, the uniformity of symptoms both subjective and objective and especially the blood picture strongly suggest that the mixed infection is not a haphazard one, but that it is due to certain pretty definite types. The types of bacteria associated with the typhoid bacillus may

very likely determine the severity and the outcome of the disease. Caulfeild has attempted to associate certain bacterial species with hemorrhage in the course of pulmonary phthisis. It is entirely possible that perforation of the intestine may be peculiarly favored by the association in the mixed infection of some organism like the streptococcus.

PNEUMOCOCCUS.

The pneumococcus is the chief cause of typical lobar pneumonia. Consolidation may also be due to certain other organisms such as the bacillus of Friedländer, the streptococcus, and the *Streptococcus mucosus*. **Pleurisy, pericarditis, empyema, peritonitis, otitis media, conjunctivitis, serpiginous ulcer, metritis and pyosalpinx, abscesses, septicemia, and pyemia** may all be due to the pneumococcus.

For the isolation of the pneumococcus, agar containing blood or blood-corpuscles is the medium of choice. If the sputum has not been collected with great care it is better to rinse little masses of it in sterile salt solution before making smears upon the plates. The pneumococci appear as small colonies considerably pigmented and by transmitted light very much darker than the other colonies. In isolating the pneumococcus from sputum, one may possibly obtain avirulent strains from the throat rather than the strains from the lungs. If the strain causing the disease is virulent this difficulty may be obviated by injecting the sputum subcutaneously or intraperitoneally into a rabbit (a mouse is frequently as satisfactory). The rabbit generally dies within twenty-four hours if

at all, and pure cultures may be obtained from the heart's blood.

In addition to these methods blood-culture has been recommended. Blood-cultures are generally successful only in the early stages of the disease, however. If great care is used lung puncture may be made without the slightest harm to the patient. But this method may also fail. It has an advantage in common with blood-cultures in that, with careful technique, any growth occurring is likely to be pure and may be of service in a minimum length of time for the preparation of an autogenous vaccine. If the bacteria are isolated from the sputum the danger of getting avirulent strains from the throat must be taken into consideration and it is a question as to whether such a vaccine will be more useful than a good polyvalent stock vaccine.

Washburne and Eyre (Lancet, vol. i, pp. 19-21, 1899) first called attention to the fact that there are apparently several distinct types of the pneumococcus. This observation was confirmed and exact evidence furnished by Neufeld and some of his pupils. Neufeld and Händel (Arb. a. d. kais. Gesundh., No. 34, pp. 294-304, 1910) have isolated at least five distinct types of the pneumococcus, none of which are capable of stimulating in a treated animal the production of antibodies antagonistic to any of the others. For this reason stock vaccines which must be used in the majority of cases of lobar pneumonia, both on account of the time required to prepare the autogenous vaccine and also for reasons of economy, should be polyvalent; that is, they should contain all the types of

pneumococcus known or at least the more common ones.

The whole subject has been so ably reviewed recently by F. E. Stewart (Medical Record, Aug. 17, 1918) that we take the liberty of utilizing much of his own text. This step is further warranted by the fact that his purpose is mainly to aid the practitioner who cannot always avail himself of laboratory diagnostic method—one of the aims of the present work.

Summarizing the subject, as elucidated by recent labors, the above writer advises the conjoint use of **both serum and vaccine** in the same patient. In respect to the former he urges as the most important fact to remember is the necessity of prompt action and the use of large initial dose (100 c.c.) and repeated injection, for the purpose of destroying the infecting micro-organisms, neutralizing their toxins, and keeping the blood sufficiently loaded with antibodies to prevent reinfection.

Concerning the serum treatment of streptococcus pneumonia, the researches carried on at the Base Hospital, Fort Sam Houston, San Antonio, Texas, by various medical officers, Major J. G. Cumming, Lieutenant C. B. Spruit, and Colonel Charles Lynch (Jour. Amer. Med. Assoc., Apr. 13, 1918), for the purpose of considering the pneumonia situation, proved of great value. Of patients with pneumonia following measles, 28 blood specimens in all were tested. Of these, 24 were negative while 4, or 17 per cent., were positive for hemolytic streptococci. In the series of necropsies reported, a much larger percentage of the specimens were positive. Of the 61 examinations of pleural exudates from patients in the pneumonia wards, organisms were found in 48 specimens.

Of 41 lobar pneumonia specimens, 59 per cent. proved to be pure streptococcus, and 41 per cent. pneumococcus. Of 7 bronchial pneumonia specimens, 86 per cent. were streptococcus, and 14 per cent. pneumococcus. By consolidating these two groups, the authors found that 63 per cent. were hemolytic streptococci and 37 per cent. pneumococci. In the 31 necropsies, streptococci were isolated from 21 lung specimens, 22 pleural exudates, 14 pericardial exudates, and 15 hearts' blood specimens. The streptococcus was isolated in each of the 24 bronchopneumonia cases. Of these 24 cases, 18 or 75 per cent. are known to have followed measles. In only one necropsy on a patient that had had pneumonia following measles was a type epidemic pneumococcus found, and this was coexistent with the hemolytic streptococcus; while in the 7 lobar pneumonia cases, hemolytic streptococci were found, either in pure culture or coexistent with pneumococci, in 5, or 71 per cent., of the necropsies.

The authors state: "It would appear that the hemolytic streptococcus was the cause of death in 29, or 94 per cent., of the 31 cases of lobar pneumonia included; and since this organism was found in entirely pure cultures in all lung specimens, as well as in pure cultures in either serous exudates or the hearts' blood or both, in cases of pneumonia following measles, it may be concluded that the hemolytic streptococcus is the causative organism in this complication following measles; moreover, that it was the immediate cause of death in a large percentage of the so-called lobar pneumonia cases."

It was then deemed permissible to conclude that on account of the unquestioned prevalence of streptococcus

pneumonia, both as a complication of measles and as coexistent with lobar pneumonia, it is apparent that a new differential procedure for type identification must be devised. In none of the lobar pneumonia cases which at necropsy showed both pneumococci and streptococci, had an ante-mortem diagnosis of type epidemic pneumococci other than Type IV been made.

Because streptococci were found in 55 per cent. of the cases, because mortality from infection by the streptococcus is high in the so-called lobar pneumonia cases, and because the streptococcus has not heretofore been recognized as an important factor in the pneumonias, the authors consider the identification of this organism in the sputum of great importance in determining the proper therapeutic treatment and say that some of the failures of the antipneumococcic serums in the treatment of lobar pneumonia are doubtless due to the hemolytic streptococcus. Therefore they advise that a specific antistreptococcus serum of a high titer be applied to both groups of pneumonias, believing that this will be the most effective agent in reducing the high mortality.

The results of the researches of Cumming, Spruit, and Lynch at Fort Sam Houston, were verified in essential particulars by the report of the commission sent by Surgeon-General Gorgas to Texas in February to study the pneumonia existing there. This commission was composed of R. Cole, W. G. MacCallum, O. T. Avery, A. R. Dochez, R. A. Kinselle, F. G. Blake, T. M. Rivers, H. John, F. A. Stevens and William C. Von Glahn, all of the U. S. Army.

They found that pneumonia occurred frequently in the camp, but not al-

ways as a sequel of measles; that the coryza, conjunctivitis, and laryngitis produced by measles appeared to predispose to infection of the respiratory tract with bacteria; that streptococcus infection might occur in a person who had not had measles, and it is quite probable that other diseases, such as scarlet fever, predispose to it in the same way as measles. MacCallum says "When *Streptococcus hemolyticus* gained a foothold it usually caused in this series of cases the anatomic complex called here 'interstitial bronchopneumonia.' This is the same whether it is preceded by measles or scarlet fever, or by other diseases, and its characters are due to the specific effects of the streptococcus. When lobar pneumonia followed measles, the pneumococcus was in this series accompanied by the streptococcus, and in some cases the lobar pneumonia was complicated, anatomically, by the corresponding bronchopneumonia."

It was also observed that infection with the hemolytic streptococcus does not always cause an interstitial bronchopneumonia, but may produce a patchy lobar pneumonia.

Another late contribution to the bacteriology of the pneumonias is the report of G. F. Dick, M.D., (Journal of the A. M. A. for May 25, 1918). It is based on 60 cases admitted to the base hospital during February and March. The evidence obtained by examination of the sputum was further substantiated in a number of cases by bacteriological examinations of the blood during life and of the lungs after death. This report confirmed the statements of the other investigators quoted in relation to the frequency of the streptococcus as an etiological factor in pneumonia.

The pneumococcus cases form 48

per cent. of the 60 cases studied; of these 21 per cent. were Type I, 34 per cent. Type II, and 45 per cent. Type IV. Only one case of Type III was observed. In 46 per cent. of the cases streptococci were the predominating organisms; of these 46 per cent. were non-hemolytic. In the cases coming to necropsy the pneumonia in which this type of organisms was found resembled the ordinary pneumococcus lobar pneumonia. This series of cases is interesting on account of the high percentage of streptococcus infection particularly due to the non-hemolytic organisms, which were also found associated with cases diagnosed as influenza and in the pus from appendicitis.

As to the *vaccine treatment of the pneumonias*, in 1912 Sir A. Wright undertook some investigations for the purpose of testing the value of bacterial vaccines in the prophylaxis and treatment of the disease. These investigations were carried on in the South African gold and diamond mines. At this time the existence of definite groups of the pneumococcus, distinct and possessing specific immune reactions, had not been definitely proved, so it is not known what groups of the pneumococcus were included in the vaccines he used. The results of these investigations (*Lancet*, April 13, 1918) were valuable, as the remarkable reduction in the mortality of pneumonia among the native mine-workers fully demonstrated.

F. S. Lister found that the pneumonia prevalent among the workers in the diamond mines at Kimberley, South Africa, was due mainly to three groups of pneumococci. (Publication 10, South Africa Institute for Medical Research, 1917, and *Jour. Amer. Med. Assoc.*, April 20, 1918), that "three

subcutaneous inoculations with the triple vaccine of the three groups prevent the occurrence of pneumonia as caused by members of these groups, but not the pneumonia due to other groups of the pneumococcus." From 7 to 10 million of pneumococci were given at each injection, the cocci being first killed by a germicide and not by heat. He also found that his own serum, following vaccination, contained agglutinins and opsonins, against the type of organism injected, eight months after the last inoculation.

Various other investigators have reached very similar conclusions. Cumming, Spruit, and Lynch, to whose report reference has already been made, consider it advisable to vaccinate measles patients found to be hemolytic streptococcus carriers, and also advise vaccination against the streptococcus irrespective of measles patients, because the hemolytic streptococcus is of such universal prevalence, that such universal vaccination would protect against the infection. If this procedure was carried out they hold that the case rate, as well as the mortality of the pneumonias, both pneumococcus and streptococcus, would be reduced by a large percentage. They suggest the use of a triple vaccination for this purpose, consisting of the hemolytic streptococcus and pneumococcus Types I and II.

E. C. Rosenow, of the Mayo Foundation, Rochester, Minn., reported results in the treatment of 200 cases of pneumonia with a partially autolyzed pneumococcic vaccine. He recommends (*Jour. Am. Med. Assoc.*, Mar. 16, 1918) that a polyvalent vaccine prepared in this manner be injected in all cases of lobar pneumonia as soon as the diagnosis can be made.

Mixed vaccines were opposed for a time by some of the specialists in vaccine therapy, also the use of stock vaccine, but more recent investigations have removed much of the prejudice. Castellani, was one of the first to emphasize the importance of mixed stock vaccines. For a number of years he advocated the mixed vaccine of typhoid and paratyphoid A and B. Not only did he advise the use of mixtures of typhoid and paratyphoid, but also suggested the addition of the microbes causing cholera, plague, and Malta fever. He furnished data to show that agglutinins developed in the serum as a result of the inoculation of such mixed vaccines were not less than when the vaccines were given separately. (Cited by A. Fleming, Practitioner, April, 1917.)

Although this applies to diseases other than the pneumonias, it emphasizes the value of polyvalent vaccines, a fact confirmed by many observers. Bearing directly on pneumonia, however, is the testimony of S. Solis-Cohen (Med. Record, Apr. 27, 1918), who states that at Fort Oglethorpe, A. Dare and D. H. Bergey had treated pneumonias with a mixed vaccine and in over 100 cases of lobar pneumonia the death rate had been less than 6 per cent. Stewart recommends:—

1. Antipneumococcic and antistreptococcic serum conjointly, employing the polyvalent serum, assuming that the patient is probably suffering with a mixed infection. 2. A polyvalent vaccine made from as many strains or types of the pneumococcus and streptococcus as it is possible to obtain; preferably a sensitized vaccine, because the first step in the immunizing process has already been accomplished outside of the patient's body. The im-

munizing response is then more rapid and complete, while there is less likelihood of severe reaction. 3. Both serums and vaccines in the treatment of the same patient.

W. E. Robertson, C. P. Brown, and A. G. Beckley (N. Y. Med. Jour., Oct. 21, 1916) tried **serobacterins** intravenously in a series of cases. Of 11 cases, some received a polyvalent bacterin composed of sensitized pneumococci alone, others a mixture of sensitized pneumococci, streptococci and staphylococci. Those receiving the mixed bacterin reacted with a chill and a rise in temperature. Of the 11 cases, 10 ended in prompt recovery. The eleventh died of nephritis.

V. C. Vaughan has studied the question of pneumonia in the various camps, according to Hitchens (Trans. College of Phys. of Phila.; Med. Rec., Aug. 17, 1918), and found a law in regard to the incidence of death rate from pneumonia. Pneumonia in the tropics is a very serious disease and is more prevalent in the South than in the North. A vivid picture of conditions was presented by two southern camps, only 200 miles apart, showing different mortality and morbidity rates. This difference was based on the communities from which the men came. The rates were, however, lower than they were in their home cities. There is also a variation in the death rate according to the situation in relation to the Mason and Dixon line and the Missouri River. North of this line the death rate is lower; south of it, higher. If the men came from Florida and Georgia, the incidence of pneumonia was high. In one camp the negroes came from families who had been north for two or three generations. The death rate was no higher than for white men, and not

so high as for the white troops from the South. Col. Vaughan found that during the Civil War the death rate was 18 per thousand per year for the Northern troops, and 63 per thousand per year for the Southern troops. Therefore, the further south the location, the greater the virulence of the disease. Although the immunization against pneumonia lasts but a few months, it is well worth while.

Prophylactic Vaccination Against Pneumococcus.—A definite immune response has been secured to types I and II, and little or none to type III in persons vaccinated against the pneumococcus. It remains to be determined how long this immunity persists.

At Camp Upton, as reported by Cecil and Austin (*Jour. of Exper. Med.*, July, 1918) 12,519 men were vaccinated against pneumococcus types I, II and III. Three or 4 doses were given at intervals of 5 to 7 days.

During the 10 weeks that elapsed since the vaccination, no cases of pneumonia of these 3 types occurred among the men who had received 2 or more injections of vaccine. In a control of approximately 20,000 men there were 26 cases of pneumococcus types I, II and III pneumonias during the same period. The incidence of pneumococcus type IV pneumonia and streptococcus pneumonia was much less among the vaccinated troops than among the unvaccinated.

Small sterile infiltrations disappearing spontaneously occasionally follow the injection of large doses of pneumococcus vaccine and appear to be an expression of cutaneous hypersusceptibility. The persons who develop these lesions exhibit local reactions to each dose of vaccine. They also give abnormally marked reactions to intrader-

mal injections of pneumotoxin. They do not, however, exhibit anything notable in the agglutinative or protective powers of their serums after vaccination. Whereas the immune response is characteristically specific for the type of pneumococcus, this reaction is not specific for any type. The writers found no evidence that type III is more prone to elicit these severe local reactions than are types I and II. Prophylactic vaccination against pneumococcus of types I, II and III is practical and apparently gives protection against pneumonia produced by these types.

In the recent epidemic of **influenza** the development of bronchopneumonia was associated with such a high mortality as to be the cause of a panic which, according to E. A. Fennel (*Jour. Amer. Med. Assoc.*, Dec. 28, 1918), was evidenced in the use of a variety of unjustified therapeutic and prophylactic measures. The causative organism of the influenza is not yet definitely known, but it seems clear that the disease, when uncomplicated, runs a brief and mild course with recovery. The investigations into the organisms associated with the development of the serious bronchopneumonia agree in showing the almost constant presence of pneumococci of the fixed and heterogeneous types, and of streptococci. The present possibilities of prophylaxis, therefore, resolve themselves into the prevention of the pneumonia. The work of Dochez and his associates in America, and of Lister in South Africa, proved the efficacy of prophylactic vaccination against Types, I, II, and III, against which practically complete protection is obtainable. Such inoculation also gives some measure of protection against the

heterogeneous types and against the streptococci, probably by virtue of the introduction of foreign protein. The saline pneumococcus vaccines, while thoroughly effective, have certain disadvantages, among which are their rapid deterioration, the necessity for the use of 3 or more doses at weekly intervals, and the occurrence of reactions following their use. These disadvantages can, however, be almost completely overcome by the use of a lipovaccine, which, though more difficult and more costly to prepare than the saline vaccine, is almost nontoxic and can be made so concentrated as to be effective in a single administration.

Empyema.—Mixed infections are a very common cause of empyema, although the exciting cause may have been the pneumococcus. The other organisms found are streptococcus, staphylococcus, the *Bacillus coli*, and sometimes the *Bacillus pyocyaneus*. Other organisms are found less frequently. In view of this fact, it would seem advisable in a case where surgical interference is necessary to attempt to raise the patient's opsonic index by the use of a mixed vaccine before the operation. It is thought that with the higher bacteriotropic power of the blood greater benefit results from the operation. This is due to the fact that the local changes in the blood-supply bring the bacteriotropic substances into more intimate contact with the infecting elements. Such a method of treatment is probably more effective than postoperative vaccination when the bacteria have built around themselves certain barriers enabling them to resist the antibacterial powers of the body fluids.

Floyd and Worthington (Bost. Med.

and Surg. Jour., vol. clviii, p. 75) have reported positive results in the treatment of empyema. Five hundred million pneumococci were given to 1 case. Improvement was noted. In three weeks the sinuses were almost closed and soon after the child was sent to the country entirely cured.

Ross (Can. Jour. of Med. and Surg., vol. xxviii, p. 189, 1908) has had a similar experience. In less than two weeks the discharge had entirely ceased and the sinuses completely and permanently closed.

Pastore (Jour. Amer. Med. Assoc., from *Pediatrics*, Sept., 1918) tried diplococcus vaccine in 8 cases of protracted pneumococcus infectious processes, pyothorax, interstitial pneumonia or migratory pneumonia. Acute pneumonia runs too brief a course for vaccine therapy to display much efficacy, but in these practically chronic cases the pneumococcus lesions in the pleura or the parenchyma of the lung were favorably influenced by this systematic intravenous vaccine therapy. The results were particularly striking in purulent pleurisy. The vaccine seemed to arrest the process and it retrogressed, obviating the necessity for operative measures and even puncture. The little patients were 18 months, 2 and 4, to 9 years old. There was usually a vigorous reaction to the first injection, with a chill, dyspnea and cyanosis but the following injections seldom elicited any appreciable reaction. In others the reaction appeared with the second or third injection, but there were no mishaps of any kind. The vaccine was a suspension of a twenty-four hour culture of Fränkel's diplococcus on a hemoglobinized culture medium. The bacilli were estimated by the opacity of the fluid, and from 0.10 to 0.20 c.c. was

used, containing from 10,000 to 20,000 of the microbes. Up to 11 injections were made in some of the children.

STREPTOCOCCUS.

Streptococci, after the staphylococci, are among the most widespread pathogenic or semipathogenic organisms. They are frequently the cause of pyogenic infections and are very common as accessory organisms in many mixed infections. They may cause inflammation and suppuration in any part of the body. Severe grades of anemia are also associated with some streptococcal infections, undoubtedly due to a hemolytic substance which is one of the metabolic products of the growth of certain types.

Great difficulty in the clinical use of antistreptococcic serums and vaccines is caused by the existence of an almost infinite variety of types within the genus. A serum or stock vaccine prepared with one variety may have no effect in the treatment of a condition caused by another one. Experience has shown that stock streptococcus vaccines are at best valuable only as a temporary measure until an autogenous vaccine can be prepared. That the serum has antistreptococcal power can be readily demonstrated by animal experimentation and by bacteriotropic methods. In streptococcal infections of very severe grade with much toxemia it will probably be advisable to try injections of large doses of the serum first or in conjunction with the vaccine.

Many attempts have been made to classify streptococci by various methods according to morphology, cultural characters (especially in bouillon), staining properties, serum reactions, ability to hemolyze blood-corpuscles, pathogenicity for laboratory animals,

and, finally, ability to ferment various sugars.

The first work done with streptococci based upon their chemical powers or metabolic reactions was that of Merwyn H. Gordon (Lancet, p. 1400, Nov. 11, 1905). He used 33 chemical substances, out of which he finally chose 9 which he considered of differential value. These are spoken of as "Gordon's tests" and include litmus milk, neutral red agar, and broth containing 2 per cent. of, respectively, saccharose, lactose, raffinose, inulin, salicin, coniferin, and mannite.

Laboring under the belief that Gordon's tests were, to a large extent, empirical and arbitrary, Andrewes and Horder (Lancet, Sept. 15, 22, and 29, 1906) proposed a classification based on the consideration of the sum total of biological characters, including Gordon's tests. Their chief guide in determining the essential characters of various groups was the numerical frequency of occurrence of the different types. In their opinion the streptococci correspond to a dominant genus, that is, one marked by numerous types, none very extreme, and all connected by intermediate forms; a genus which is at the moment succeeding in the struggle for existence. Disregarding two of the groups of streptococci (*S. equinus* and *S. mitis*) as essentially saprophytic, Andrewes and Horder recognize five groups (including the pneumococcus): *S. pyogenes*, *S. salivarius*, *S. anginosus*, *S. faecalis*, and *Pneumococcus*; all other types found being considered variants of these either by defect or excess. These types Winslow recognizes with the exclusion of pneumococci, which he places with the diplococci, and the addition of the specific type which liquefies gelatin,

S. gracilis. ("Systematic Relationships of the Coccaceæ," 1908.)

When we consider the tone of finality with which later writers speak of these various classes as fixed types, attributing pathogenicity to some and denying it to others, it seems well to recall what Andrewes and Horder state in placing their lines of classification: "We would repeat that *Streptococcus salivarius* passes by insensible gradations into *Streptococcus faecalis*, the arbitrary mannite test being alone used here to separate them. Also that the distinction between this and *Streptococcus anginosus* rests only on the somewhat shadowy character of length of chain and lesser virulence"; further, "The type which we include under this heading (*anginosus*) is, as we have explained, merely a long-chained form of *salivarius*, of somewhat greater virulence and resembling *Streptococcus pyogenes* in its hemolytic power." It is especially emphasized that no single character can be taken as a basis for classification. Taking just the question of length of chain, type "pyogenes" includes variants from long to medium; type "salivarius," from short to medium; type "anginosus," from long to medium; and type "fæcalis," from short to long. It is indeed "a somewhat shadowy character."

Also it is well known that, in a single strain, neither the hemolytic property nor the length of chain is a fixed character. Although there is a distinct tendency toward the continuance of a certain appearance on poured blood-plates, still there is a slight unaccountable variability besides that due to recognizable difference in medium. This is mentioned by Anthony in the "Collected Studies from the Research Laboratory" (New York City, 1907).

In length of chain also, as in hemolytic power, a certain culture may show a tendency; but, as Andrewes and Horder have themselves pointed out, "In one and the same culture chains of the most varying length may be found; the length of the chain may vary according to the chemical composition of the medium in which the coccus grows, and may vary on subculture."

To take these classifications, therefore, and conclude that a long chain, hemolytic streptococcus which ferments saccharose and lactose is the pyogenic variety, or even to say that it is the pathogenic type, is to make a statement that cannot by any means be substantiated at the present time. In the preparation of the vaccine the practical conclusion to make is that autogenous vaccines are nearly always necessary and, no matter what the types of streptococcus found in the lesion, it is the pathogenic organism for that case. In plating out the infectious material it must be remembered that there may be more than one type of streptococcus present and several typical colonies should be fished from the plate.

Local Infections.—Beebe and Medalia (Bost. Med. and Surg. Jour., 111, 85, 1908) report a case of **abscess** in the neck due to streptococcus, which they treated with vaccine. Two doses of 50 million each were necessary to effect complete cure. At the time of the first injection the patient was weak, exhausted, pale and emaciated, and suffering considerable discharge from the wound. A week after the injection the discharge had ceased, and the wound was nearly closed. A week after the second injection the wound was entirely healed, with no induration around it. Four weeks later the patient was entirely

well. Good results have also been recorded by Gildersleeve and also W. Hale White.

In streptococcic **adenitis**, streptococcus pyogenes vaccine is recommended by the Committee of the Amer. Med. Assoc. (Jour. Amer. Med. Assoc., Apr., 20 *et seq.*, 1913).

Vaccination against infection of **wounds** is advocated by Bielonovsky (Russky Vrach, xvi, No. 3, 1917), after noting a favorable effect in the wounded treated with injections of Wright's vaccine to protect against streptococcus infection.

In the treatment of **war wounds** with a sensitized autogenous vaccine, lipovaccines and ether-sensitized vaccines, at the Virval Belgian ambulance, in charge of Professor Depage, the efficacy of the vaccine was shown most conclusively, according to C. Levaditi (Presse méd., Jan. 30, 1919). In wounds of soft parts known to be infected with streptococci and requiring further operative measures, after the vaccine had been given, the healing occurred smoothly without infection in 95.5 per cent. of the cases, as against 93.5 per cent. successful cases among those known to be free from streptococci. With the vaccine to supplement the other measures, results as satisfactory are obtained with streptococci infection as without it except that healing takes longer. Generally, from 20 to 60 days in the graver cases are required before the wound can be definitely sutured. The dose of vaccine is 0.5 or 1 c.c. injected into the deltoid muscle and repeated every 5 or 6 days on alternate sides. The 24 hours broth culture of hemolytic streptococci is centrifuged and the sediment, in suspension in 10 c.c. (2½ drams) of

isotonic salt solution, is mixed with 4 c.c. (1 dram) of a mixture of ether and chloroform in equal parts. After 12 hours the ether-chloroform is decanted, and the suspension of the microbes is mixed with 4 c.c. of anti-streptococcus serum. After 4 hours of contact at 38° C. the whole is centrifuged and the sediment is suspended in 10 c.c. (2½ drams) of saline. After testing for sterility, it is injectable in the dose of 0.5 or 1 c.c. The intradermal test proved very instructive, the reaction being found most pronounced in the cases tending to healing, testifying to a vigorous defense on the part of the organism. In the cases of grave septicemic infection there was little or no local response to the intradermal test, hence the response to the test is a useful guide as to when the wound can be safely sutured.

In **infected gunshot injuries of the shoulder and elbow joints**, Swan (Lancet, Apr. 7, 1917) regularly gives an injection of a mixed polyvalent streptococcus and proteus vaccine, and the area is carefully röntgenographed for any bony injury and the presence of metal fragments.

Erysipelas.—Harris (Practitioner, p. 647, 1908) reports the use of streptococcus vaccine in a case of erysipelas. At the time of the first inoculation (the sixth day of the disease) the patient was very seriously ill, with a temperature of 105.4°, pulse 140, and respiration 45. A crisis was precipitated by the injection and fourteen hours later the temperature dropped to 98.8°.

Three cases of erysipelas treated by streptococcus vaccine are reported by Duncan and Illman (N. Y. Med. Jour., 11, 552, 1908). Only one dose

(30 to 60 million) was given in each case. In the first case, one of facial erysipelas, fall of temperature occurred twelve hours after the inoculation of 50 million organisms. In this case the injection was given on the sixth day of the disease. In the second case the injection, administered on the third day, when the patient's condition was becoming worse, caused rapid improvement. *Streptococcus vaccine* was given to the third patient at a time when inflammation, following tonsillitis, had begun to spread rapidly over the chest and arms, causing a temperature of 105.2°, frequently accompanied by delirium. Within twenty-four hours the temperature dropped considerably, reaching a point almost normal on the third day, and normal on the fourth.

Schorer (*Amer. Jour. of Med. Sci.*, i, 728, 1907) reports 37 cases of erysipelas treated with streptococcus vaccine. The dose varied from 25 to 100 million. In cases receiving the smaller dose desquamation appeared three days after the injection. Those receiving 100 million showed desquamation in two and one-half days. The migratory form of the disease, probably not induced by the injection, occurred in 8 cases. Three patients died of complications. In the other cases the vaccine seemed to cause shortening of the course of the disease and improvement of local conditions. According to Schorer, the opsonic index rises until the third day of the disease, then gradually falls.

Ross (*Jour. Amer. Med. Assoc.*, March 6, 1909) reports 50 cases in which vaccine treatment was administered. Though blood examination was necessary in certain severe cases,

the author considered it unnecessary to make an autogenous vaccine in every case and recommends the use of a stock vaccine made from several different strains and as many different cases as possible. The dose used by him was 10 million killed streptococci when first starting treatment, or 20 million if the case was not severe. If improvement occurred (and it usually appeared in less severe cases on the day after the injection) 10 million more were administered; if no improvement followed, only 5 million were given at the second injection. Repeated injections of 5 to 20 million streptococci were given every second day till a week after the temperature had reached normal and the erythema had subsided. Injections were given at a distance from the inflammatory area. They lessened the severity of the disease, prevented spreading of the lesions, and hastened recovery.

The writer used both autogenous and polyvalent stock vaccines in 30 cases of **erysipelas** and concludes that they hold an important place in its treatment by shortening the duration and preventing recurrence. Walters (*Amer. Jour. of Dermatol.*, July, 1912).

Chorea Minor.—Camisa (*Cent. f. Bakt.*, p. 99, Dec. 31, 1910) believes that streptococcus was the causative factor in certain cases of chorea minor studied by him. Though he does not wish to deny that in some cases chorea may be caused by other bacteria, as, for instance, staphylococci, he goes into some detail to prove the direct pathogenicity of the streptococcus in these cases. The type found was a diplostreptococcus, appearing

in short chains, of constant morphological and cultural characteristics. The numbers present appeared in inverse ratio to the severity of the symptoms, and the blood of the patients showed agglutinating properties for it, not absolutely specific but greater than for the ordinary pyogenic streptococcus. In those cases in which the blood-cultures were negative the author believes the organisms had already disappeared from the blood-stream and had invaded the nervous tissue of the cerebrospinal system, and there set up an inflammatory process. Such lesions were discovered by Nauwerck, Pianese, Guizzetti, Cesaris-Demel, Reichardt, and also by the author in 2 fatal cases of chorea.

Septicemia and Endocarditis.—The results of vaccine treatment in various types of septicemia and endocarditis have been generally favorable. Of course, this has been particularly true when it has been possible to use autogenous vaccines.

Callison (Post-Graduate, vol. xxvi, No. 5, pp. 553-554, May, 1911) reports a case of streptococcus mixed septicemia clinically resembling typhoid fever. The general clinical picture in this case combined with a Widal reaction in which there was partial clumping after three hours led to a clinical diagnosis of typhoid fever. To confirm this diagnosis it was decided to make a blood-culture. The feces were also examined, but gave negative results. Examination of the blood-culture showed a pure growth of *Streptococcus mucosus*. An autogenous vaccine was prepared and an initial dose of 400 million given. Three additional doses of 800 million

each given at intervals of forty-eight hours resulted in a normal temperature, and the patient made an uninterrupted recovery.

Terry (Post-Graduate, vol. xxiv, No. 10, Oct., 1910) treated a case of streptococcic infection following operation. The streptococcus was isolated from blood-culture; 40 million killed streptococci were given as the initial dose. The next day 165 million, two days later 300 million, five days later 300 million were given. This dose was repeated every fourth day for a period and then 600 million were given. The temperature dropped to normal after the first injection and rose twice afterward, once due to abscess formation on the left leg. Another abscess developed due to a mixed infection for which a mixed vaccine was prepared.

A case of mouth infection due to a streptococcus was described by K. W. Goadby before the Royal Society of Medicine (June 1, 1910). The patient was taken suddenly ill with shivering and with pain in the mouth. "The gums in the upper and lower jaws were turgid, edematous, and purple; there was no previous history of any disease of the mouth; the temperature rapidly ran up to 103° F., and on one occasion touched 104½° F." Streptococcus and staphylococcus were found in the mouth, together with many other bacteria. Blood-culture showed a few streptococci which proved to be identical culturally with the type isolated from the mouth and to resemble closely the form described by Andrewes and Horder as the *Streptococcus faecalis*. Autogenous vaccines were given; the initial dose was 100 million and future doses were

controlled by opsonic-index readings. Recovery took place gradually, three abscesses appearing during its course in different parts of the body. Pus from these showed the presence of the original streptococcus.

W. H. White (Proc. Roy. Soc. Med., May 25, 1910) described an instance of remarkable cure in a case of **septicemia**. The patient was a woman, aged 30, who had been taken ill with arthritis in the right shoulder, and a temperature of 105.6° F. The case was one of general septicemia following upon a small scratch on the hand. Severe septicemia developed rapidly, with arthritis in many joints, and constantly high temperature. There were various swellings about the body. One that appeared in the middle of the right arm was incised and a culture of streptococcus pyogenes isolated from the serum that oozed from the incision. Injection with a vaccine prepared from this culture was followed within forty-eight hours by a drop in temperature. There was no further rise and recovery was complete.

In the same discussion before the Royal Society of Medicine, Harold A. des Voeux described a case of middle-ear infection which he had attended. The patient was a boy who had had successive attacks. There was a clear discharge from the ear, which yielded a pure growth of streptococcus. An autogenous vaccine was prepared and administered to the patient. Des Voeux stated that the patient had remained well ever since, though the treatment had been commenced two and a half years previously to the time at which he was making this report.

In 50 cases of **septicemia** observed

by the writer antistreptococcic serum proved unavailing. Autogenous vaccines were then tried in 13 in addition to the regular treatment; 7 of these patients recovered. Abderhalden (Amer. Assoc. Immunol.; Jour. Amer. Med. Assoc., July 15, 1916).

Among the cases reported by Arthur Latham before the Royal Society of Medicine (June 8, 1910) were two of streptococcic infection. One was a long-standing case of **bronchiectasis** in which large amounts of evil-smelling pus were expectorated daily. At the time vaccine treatment was started the lungs were too badly affected to be cured. But the expectoration lost all odor, becoming bronchitic in character, and the patient was able to return to her work. The causative agent was identified among seven micro-organisms by the use of the opsonic index taken at rest and after exertion.

In a report before the Association of American Physicians, May 11, 1909, Thompson stated that he had used streptococcus vaccine with effectiveness in several cases of septicemia. The dose used was 50 million to 300 million at intervals of two, three, or four days according to the circumstances of the case. Of 7 cases of **septic endocarditis** 3 were cured, the type being one in which the author had never before seen recovery take place. In other cases which ended fatally, due to complications such as tuberculosis or pneumonia, there was evidence that the septic process had been checked by the vaccine. There was some improvement, such as fall in temperature, in all cases in which homologous vaccines were used. Several patients who came under treatment after months of ill-

ness, and in whom a fatal issue seemed imminent, gave signs for many weeks of arrested progress of the disease.

Rosenow (Jour. A. M. A., vol. lv, No. 20, p. 1720, Nov. 12, 1910) believes that the continuation of the infection in chronic infectious endocarditis is due largely to a process of immunization and adaption of the bacteria to the antibodies of the host. He has found that the bacteria grow more readily in the patient's serum than they do in normal serum. When they are grown in the patient's blood or serum they acquire a resistance to phagocytosis and a resistance to intraphagocytic destruction, and they also produce alterations in the serum which rob the leucocytes of something they need to bring about digestion of the bacteria after they have been ingested.

A case reported by Latham before the Royal Society of Medicine (*loc. cit.*) was one of malignant endocarditis. A streptococcus was isolated and a vaccine prepared by suspension in a fluid isotonic with the blood. A dose of 1 million streptococci thus prepared was given by mouth, early in the morning, when the stomach, being empty,

could absorb the vaccine. The temperature became normal and the patient's general condition improved greatly. The patient's blood was tested with this streptococcus, both before and after vaccination. In the first instance it did not agglutinate the streptococcus, but twenty-four hours after the oral administration of the vaccine marked agglutination was present.

In the experience of Irons, ulcerative endocarditis due to the staphylococcus, streptococcus, pneumococcus, and gonococcus has been exclusively treated by autogenous vaccine, but the results in the majority of cases have been unfavorable. Occasionally transient improvement is seen, but usually the inoculations have failed to stay the course of the disease.

Septicemia, puerperal.

In "A Résumé of Vaccine Therapy" (Amer. Jour. Med. Sci., Feb., 1911) H. W. Stoner has brought together the reports of various physicians concerning the results of the use of vaccines in treatment. The following list of cases of puerperal sepsis thus treated shows especially favorable results:—

Authors.	Cases.	Cured.	Improved.	Remarks.
Lloyd	2	0	2	1 not benefited
Floyd	1	1	0	
Richardson	2	1	0	
Bristow	2	2	0	
Martyn	1	1	0	1 not benefited
Crowe	1	1	0	
Turton	3	1	1	
Strubell	1	0	1	
Oastler	2	1	0	1 not benefited
Leary	47	43	0	
White	1	0	0	4 not benefited Not benefited
Hartwell	18	18	0	
Hoobler	3	3	0	1 not benefited
Oastler	2	1	0	
Sherman	1	1	0	
	87	74	4	9 not benefited

Hartwell, Streeter, and Green treated 97 cases of sepsis with bacterial vaccines (Surg., Gyn., and Obst., 271, 1909). Bacteriological examination was made first in all cases, the character of the vaccines being then determined by the character of the infection. The initial dose varied from 5 to 25 million. Further increasing doses were given at intervals of four days. In some cases antistreptococcic serum was used previous to inoculation with a streptococcic vaccine. But it was concluded that, in general, better results followed the use of the vaccine alone. There were 24 cases of general infection, 18 of which were puerperal, and 41 cases of local sepsis (25 streptococcic). All of these cases recovered. The authors recommend that bacterial vaccines should be employed in cases of puerperal infection in which there is not prompt response to routine treatment, and especially in cases in which the disease has remained stationary for some time.

In the treatment of puerperal sepsis Van Cott especially recommends the use of a polyvalent vaccine containing streptococci, staphylococci, and colon bacilli (Long Isl. Med. Jour., editorial, 219, 1909). Results from the use of this are very good in the majority of cases and much time is saved which would be wasted if vaccine treatment were withheld until an autogenous vaccine could be prepared.

Lloyd (Intercolonial Med. Jour. of Australasia, 1907) treated with a mixed streptococcus and staphylococcus vaccine 2 cases of puerperal sepsis, found to be infected with both types of organisms. In the first case there was a temperature of 105° and a pulse of 136 on the eighth day after

delivery. An injection of 25 million streptococci and 250 million staphylococci was given. The quantity was doubled every two days for two weeks. On the fortieth day, the patient was sufficiently improved to leave the hospital. In the second case there was a temperature of 103° and a pulse of 168. The two species of cocci were found in a culture from the uterus, which was then swabbed with 2 per cent. formalin and packed with iodoform gauze. Since instead of improving the patient's condition became worse, an injection of 100 million cocci was given. This was followed by satisfactory progress.

J. A. Beruti (Revista de la Asoc. Med. Argentina, June, 1917) concludes as to specific vaccine therapy, that it has not sustained its promise. Vaccines made with other bacteria have proved unexpectedly effectual in the hands of some, especially in Argentina, with Enriquez, Kraus, Mazza and others, and Werner of Vienna has reported excellent results with a colon bacillus vaccine in puerperal fever. Beruti himself used an extract of colon bacilli, instead of a vaccine, applying it in a number of very serious cases of puerperal septicemia and with constantly unfavorable results. The intense reaction that followed the intravenous injection was unmistakably deleterious. But why they are so decidedly beneficial in some cases and so decidedly the reverse in others is still a mystery.

N. P. Costa (Rev. de la Asoc. Med. Argentina, June, 1917) regards the reaction to non-specific vaccine as a kind of anaphylactic shock, liable to do harm.

Watters and Eaton (Bost. Med. and Surg. Jour., April 13, 1911) re-

port treatment of 50 cases of puerperal sepsis with vaccines. A polyvalent vaccine was used as soon as diagnosis seemed definite and until the autogenous could be prepared. Four cases which ended fatally were beyond hope of recovery when the vaccine treatment was begun. In 3 other cases which were moribund when inoculations were begun there was possibly a prolongation of life for two or three days. Besides the above-mentioned cases there were 43 patients, 2 of whom died and 41 recovered. Of the 2 who died 1 was operated on for suspected pus-tube, which was not found, the patient dying six days after; the other was subjected to blood-transfusion, dying within a few hours.

Western (Proc. Roy. Soc. of Med., vol. v, No. 5, Obst. and Gyn. Sec., pp. 214-232, Mar., 1912) investigated 100 cases of puerperal septicemia, 56 of which were treated with vaccines. The patients were in the puerperal septicemia ward at the London Hospital; 62 per cent. of the cases occurred on the second or third day after delivery. It is interesting to note that the incidence on the second day was as great as on the third day among the fatal cases, while among those who lived the number in whom the disease appeared on the third day nearly doubled those in which it appeared on the second day. This suggests that the more virulent the infection the more rapid the onset and the more fatal the results.

In 96 cases in which blood-cultures were examined a positive result was obtained in 39 (40 per cent.); 36 of these contained streptococci. Cultures were taken from the uterus in

43 cases, in 31 of which streptococci were grown in pure culture. In only 7 cases were the results completely negative, and there is reason to believe in some instances that this was due to faulty technique. Streptococci occurred in 80 per cent. of the cases examined and in 76 per cent. in pure culture.

Wherever possible an autogenous vaccine was used. Some cases where the stock vaccine was first used showed no improvement after several injections, but at once responded by a marked fall in temperature when the autogenous vaccine was given. The mortality rate in puerperal septicemia is about 57 per cent. In this series of cases, of the 56 treated 30 lived, while 18 died, a mortality of 32 per cent. Of the 44 cases untreated 20 lived, while 24 died, a mortality of 55 per cent.

Scarlet Fever.—Much work has been done to prove the etiological relation of the streptococcus to scarlet fever. It would be very valuable if such a relationship could be proven, as it would permit not only of specific vaccine therapy, but of prophylactic vaccination. The work done up to the present time, however, does not establish the possibility of prophylactic inoculation against scarlet fever, in spite of all of the claims that may be made for it by many Russian workers.

The first description of a streptococcus as the primary cause of scarlet fever was given by Klein in 1886 (Report of Medical Officer, Local Board of Government, 1885-86, No. 8). His was a milk-clotting organism which he called *Streptococcus scarlatinae*. It is later described by Klein

and Gordon as a conglomerate streptococcus, clotting milk, pathogenic to the mouse in ten to fourteen days; always found in the scarlatinal throat, but not in the normal one.

Andrewes and Horder (*loc. cit.*) believe that if any streptococcus is the cause of scarlet fever it is to be found either in the group *S. pyogenes* or *S. anginosus*, more probably in the latter; since these 2 are the types which they have found to predominate in such cases, and it is scarcely likely that so common an agent of suppuration as *S. pyogenes* would be the primary cause of a specific communicable disease.

Gabritschewsky (Russ. Vrach, No. 30, 1905) reported success from the prophylactic use of a vaccine prepared from bouillon cultures of tonsillitis and scarlatina streptococci killed by exposure to 60° C., 5 per cent. phenol being added as a preservative. The vaccination was prescribed to be practised only on healthy persons. The doses, graded according to the strength of the vaccine, approximated 0.3 c.c. for a patient 2 to 5 years of age, 0.5 c.c. for one 5 to 10 years of age, and 0.7 c.c. for one 10 to 15 years of age. Gabritschewsky claimed that three doses sufficed to establish an immunity against scarlet fever which would last six to eighteen months. Many Russian physicians following his methods claim to have accomplished wonderful success in controlling epidemics, but workers elsewhere have not been able to corroborate these results.

The general, more conservative opinion seems to be that the true etiological factor in scarlet fever is unknown, but that the streptococcus is a common and serious secondary

invader, causing many serious complications. Taking this point of view, it is easily seen that much good may be done by the use of streptococcus vaccines in the treatment of scarlet fever, and much can be hoped for in the way of prophylaxis from the immunity which may be produced against secondary streptococcic infections.

Di Cristina (Pediatria, July, 1918) prepares the vaccine from an extract of the scales, an antigen having been found in them which seems to be able to confer permanent immunity. He dissolves out the antibodies, soaking the scales in serum from convalescents. Subcutaneous injection of this vaccine induces the production of a specific amboceptor for the alcoholic extract of the desquamated scales. This showed that the reaction observed was not a simple reaction of the lipoids contained in the scales, but due to the presence of antigens. Children from 2 to 9 years old, treated with the vaccine until the immunity reaction appeared, in close contact with scarlet fever patients or with peeling convalescents, never developed scarlet fever. These experiences substantiate that the branny scales are the last stronghold of the causal germs.

Rheumatism.—Rheumatism may be divided into various types. The infectious type in which we are interested may be divided into 2 series, the acute and the chronic. Poynton and Paine, Ainley Walker and Beaton, and Beatty all agree in finding the streptococci in the acute form of the disease. In the chronic form investigators generally announce the presence of a streptococcus.

Frequent attention has been called

to the association of rheumatic conditions with diseases of the throat. Recently Max Senator (Deut. med. Woch., pp. 414-5, Feb. 29, 1912) emphasized the significance of nasal conditions in rheumatism. He considers acute articular rheumatism a subpyemia. The pyemia-form picture represented by acute articular rheumatism suggests to him merely a lowered resistance to infection and not an absolute abolition of the same. Operations on the nose and acute infections lowering the vitality of the mucous membrane seem to afford ideal conditions for bacterial invasions into the general system, while the lymphatic system of that region is especially favorable for the conveyance of bacteria (Poli, Logan, Turner, and Broeckaert, Arch. f. Laryng. u. Rhin., Bd. 22).

Billings (Arch. Int. Med., vol. ix, No. 4, pp. 484-498, April 15, 1912) has made a careful study of chronic focal infections and their etiological relations to rheumatism, nephritis, etc. The site of the focal infection may be the faucial tonsils, the peritonsillar tissues, supratonsillar fossæ, the lymphoid tissues, or membranes of the pharyngeal spaces. Abscesses of the gums and alveolar sepsis, pleuritic and pneumonic lesions, and chronic ulcers of the intestinal tract are also considered frequent sources. The genitourinary tract or gall-bladder may often be the original site of the trouble.

In 1900 Poynton and Paine isolated a diplococcus from the infected joints and from throats of patients suffering with the disease. Popoff (Med. Prebavlema k. Morskoma Sbomekie, p. 401, 1887) obtained cultures of a

micrococcus from the blood of rheumatic-fever patients. Achalme (C.-r. Soc. de Biol., Paris, 1891) described an organism resembling the anthrax bacillus which he isolated from recent cases of rheumatic fever. He could not reproduce the disease in animals by injecting his cultures. Thiroloix (Semaine méd., p. 376, 420, 1893; C.-r. Soc. de Biol., pp. 268, 882, and 945, 1896) described an identical bacillus and reproduced lesions in rabbits. Achalme's bacillus has frequently been found by other investigators and is often associated with the diplococcus. Dana (Amer. Jour. Med. Sci., p. 31, 1894), Westphal, Wassermann, and Malkoff (Berl. klin. Woch., No. 29, p. 638, 1899) all report finding a diplococcus.

Beaton and Ainley Walker (Brit. Med. Jour., pp. 237-239, Jan. 31, 1903) isolated a "*Micrococcus rheumaticus*." This *Streptococcus rheumaticus*, as it is generally called in this country, exhibits no distinct characteristics. It is a small diplococcus growing in chains; has strong acid-forming properties, fermenting dextrose, levulose, galactose, maltose, arabinose, dextrin, saccharose, lactose, salicin, and mannite. It does not ferment inulin, dulcitol, or sorbitol. It turns milk acid, but does not, as a rule, form a clot. It forms acid in bile-salt-lactose-broth precipitating the albumin and bile salts. It is said that, if the broth in which the *Streptococcus rheumaticus* has been grown is filtered, other forms of streptococci will grow well in the filtrate, whereas the same organism will not.

Fordyce ("Int. Clin.," 18th series, vol. i, p. 40) studied the opsonic index of the *Streptococcus rheumaticus* ob-

tained from patients suffering with acute rheumatism with fever, painful and swollen joints, acute pericarditis, and albuminuria. During the first day the fever and physical signs of the pericarditis subsided. The next day the index was 1.1. For the heated serum it was 4.5 as compared with 0.1 for the heated normal serum. With the patient's improvement the index rose to 1.3. Tunnicliffe (Jour. Inf. Dis., June 12, 1909) found that with marked involvement of new joints and rise of temperature the index falls, and that with improvement the index rises above normal. In a case ending fatally she observed that the index rose just before death. The index follows an identical course when tested with *Streptococcus pyogenes*.

The following is quoted from Andrews and Horder (Lancet, vol. ii, p. 782, 1906):—

"*Acute Rheumatism*.—Our data as regards rheumatic fever are not very numerous and are by no means convincing. In view of the strong claims put forward by Poynton and Paine for the *Diplococcus rheumaticus*—an organism which from all accounts appears referable to the streptococcus group—we have made a number of efforts to isolate it from the heart's blood, pericardial fluid and cardiac vegetations of fatal cases of acute rheumatism, using various culture media for the purpose. In the majority of cases our results have been wholly negative; the cultures have remained sterile. This, we gather, has also been the experience of several other observers. In 2 or 3 cases, however, we have obtained a scanty growth of streptococci; sometimes from the pericardium, less often from the heart's

blood. On testing these they did not for the most part prove in any way peculiar, and they were various in their reactions. In 1 case four or five different forms were isolated from the pericardium. The varieties isolated have been as follows:—

Streptococcus pyogenes.—Variant 1c,
twice.

Streptococcus anginosus.—Variant 3b, 3d,
once each.

" " .—Variant 3f,
twice.

" " .—Variant 3s, 3u,
3v, once each.

These, in our opinion, may well have been of the nature of terminal infections, having no necessary relation with the disease. We have entirely failed to find any one type of streptococcus which we could justly associate with rheumatic fever.

"We have had two opportunities of testing specimens furnished to us as the genuine 'rheumococcus.' One was received indirectly from Dr. Poynton and proved on testing to be the variant of *Streptococcus salivarius*, which we have classed as 2e—a very common fecal type met with twenty times by Houston. We regret that other specimens kindly promised us by Dr. Poynton have not reached us in time for incorporation with the results here published. Our other opportunity was a 'rheumococcus' sent to Dr. Bullock by Dr. Beattie, of Edinburgh, and courteously sent on to us. It proved to be *Streptococcus fecalis*, type 4a—the commonest of all intestinal streptococci. Another specimen from a case of chorea kindly sent us by Dr. Paine was unfortunately dead and could not be tested. We hope to have fuller opportunities of testing specimens of this organism in the near future.

F. M. Wood (Chicago Med. Recorder, Apr., 1917) recommends an autogenous vaccine made from *Diplococcus rheumaticus*, obtained from the oral cavity. The initial doses should be very small until the patient's resistance has been determined; it is usually best to begin with from 25 to 50 million organisms. The dose can then be doubled at the next injection and increased up to the point of producing a mild reaction. At this point it should be kept stationary for a short while and then again raised. If it is impossible to secure an autogenous culture one should begin with a stock vaccine and try to secure the culture later. In the various forms of chronic rheumatism, or arthritis, while the cause may not be primarily bacterial, there is often a secondary infection and much good will come from the use of a stock vaccine made from mouth organisms or from those secured from any focus of infection discoverable. If the first vaccine used does not succeed, another should be tried and this experimentation continued until a satisfactory one is found, or the possibilities have been exhausted. In addition to the use of vaccines in acute rheumatism one should give alkalis to overcome the tendency to acid production and calcium lactate in doses of 0.3 gram every three hours to bind the acid bodies which tend to neutralize the normal calcium of the blood and tissues.

It is probable that in rheumatic conditions and complications such as nephritis, endocarditis, etc., there are often mixed infections or secondary infections to be considered. David J. Davis (Arch. Int. Med., vol. ix, No. 4, 1912) has given this subject careful consideration in 28 cases of arthritis.

Hemolytic streptococci were obtained from the tonsils in all cases and were predominant in most of them. In many the growths were practically pure. In 2 pneumococci were found and in another the *Streptococcus mucosus* occurred in conjunction with a few hemolytic streptococci. The joint fluids and blood were invariably sterile. Perhaps the frequent finding of pneumococci in post-mortem examinations of patients dying of endocarditis may be explained as a secondary infection which has localized on the heart valves.

Dr. Lyon Smith (Glasgow Med. Jour., vol. lxxv, pp. 218-223 and 228-290, 1911) has had favorable results in the treatment of **rheumatoid arthritis**. Five cases are reported. He believes the *Diplococcus rheumaticus* has considerable claim to be considered as of etiological importance in rheumatism. Wolverton, Ball, Bannatyne and Lindsay have likewise reported satisfactory results.

GONOCOCCUS INFECTIONS.

The gonococcus is responsible for infections of various mucous and serous membranes; it may cause septicemia and endocarditis. The most common clinical manifestations of gonococcal infection are acute and chronic anterior and posterior urethritis, prostatitis, orchitis, and inflammation of other structures intimately connected with the urethra—cystitis, Cowperitis, seminal vesiculitis. In the female it is a frequent cause of vulvovaginitis, endometritis, and salpingitis. It is also the cause of serious and rapidly developing ophthalmia, especially of the newborn. Among the metastatic infections caused by this organism are gonorrheal arthritis and less frequently iritis.

H. Culver (Jour. Amer. Med. As-

soc., Feb. 3, 1917) compared 3 vaccines: gonococcus vaccine, giving 100 million killed organisms; meningococcus vaccine in the same dose, and colon bacillus vaccine, 25 million. The results were identical. Intravenous injection was followed after 20 minutes to 1 hour by a chill, with or without headache and nausea or vomiting, severe pain in the affected part, a slight fall of temperature followed by a slow rise to a maximum in from 1 to 4 hours. The temperature then fell to normal in 24 hours. No benefit was observed when the dose was insufficient to provoke the typical reaction.

Müller and Weiss (Wiener klin. Woch., Mar. 2, 1916) contend that the efficiency of vaccine therapy of gonorrhea is due mainly to the febrile reaction. Similar benefit can be obtained from any non-specific alien albumin, as shown in 40 cases in which milk or sodium nucleinate was injected intramuscularly.

Watabiki (Jour. Infect. Dis., Feb., 1918) found that the serum of patients with gonococcal infection may contain specific gonococcal precipitates, but this seems to be the case when the infection has been severe and has lasted for some time. The serum of patients with typhoid or other infections, not gonococcal, does not contain gonococcal precipitin. The serum of rabbits injected with 8 strains of gonococci contained precipitin, each one for all the different gonococci.

To the vaccine therapist the gonococcus is particularly interesting on account of its location in the tissues and its relation to the lymph supply of the infected part. In the beginning of their activities the cocci grow in the superficial epithelial cells, but soon penetrate between the cells to the deeper

layers, where they continue their irritation as the superficial cells desquamate. This fact may explain some of the failures reported to have followed the use of vaccines. There is a tendency on the part of some genitourinary surgeons to administer enormous doses of gonococcus vaccine in the treatment of **acute urethritis**—as much as 10 billion at a single dose. Such a procedure cannot yet be recommended, as data are not available. If experience proves that these amounts are not fraught with danger of metastatic trouble there would seem to be good theoretic reasons for their use. They evidently bring about sufficient local hyperemia to overcome the effort of the organisms to protect themselves from the body fluids. On the other hand, Lespinasse (Ill. Med. Jour., vol. xxi, No. 4, pp. 446-449, Apr., 1912) gives very small doses. He says that in acute cases very few favorable results have been reported, but as the disease becomes more chronic the results of vaccine therapy become progressively better. The same thing applies to acute and chronic complications. The dosage is believed to be very important and should be accurately adapted to each patient. In acute cases doses as low as a million, repeated every day, have been given with fair results. In less acute cases 5 to 10 million are given at the start. This amount is increased from 1 to 5 million at each dose, giving the doses every five to seven days. In **chronic urethritis** the initial dose is 20 million, and this amount is increased 5 to 10 million, each time giving the injections about one week apart. This author says that the importance of mixed infections is being brought out and emphasized more every day and that to reach these cases mixed vaccine should be used.

As Ravogli (Ohio State Jour. of Med., Dec., 1916) concludes that: Vaccine therapy for gonorrheal affections has a value—not absolute, but relative, to its localization and complications. Vaccination alone is not capable to extinguish the process in the urethra, but it may shorten the process if combined with local antigonorrheal measures. Antigonococcic vaccination seems more active in secondary gonorrheal localizations. The injections given under the skin or in the muscular masses cause no inconvenience, and the reaction is generally accompanied by fever. The biological reaction and the symptoms following the vaccination have no other diagnostic value as they are not constantly in accordance with the clinical symptoms. As we shall see farther on in these pages, the more recent observations of Lumb tend to modify this estimate.

Extensive researches on the removal of the endotoxins from the **gonococcus** and other organisms were undertaken by Thomson (Lancet, Mar. 8, 1919) to produce nontoxic vaccines which could be injected in sufficiently large doses to develop a great amount of immunity. The toxicity of most germs was successfully reduced some 50 to 100 times. Thus, with ordinary gonococcal vaccine it was found necessary to begin in acute cases with doses not exceeding 5 millions and gradually to increase to about a maximum of 250 millions. On the other hand, the same strains of gonococci when detoxicated could be administered in acute cases in doses of 2500 millions and increased to 10,000 millions. These large doses caused even less toxic symptoms than the small doses of the ordinary vaccine.

The therapeutic results obtained

corresponded very markedly with the serologic tests. Thus it was found that the cases which showed the highest degree of immunity as estimated by the complement-fixation test recovered much more rapidly, and *vice versa* in those which showed a low degree of complement fixation the disease ran a prolonged course. The dose of 200 millions of ordinary gonococcal vaccine produced malaise and fever in the normal subject, whereas the symptoms arising from a dose of 5000 millions of the detoxicated vaccine were scarcely noticeable and no fever was induced. Experiments have been carried out with detoxicated vaccines for the prevention and treatment of bronchial and nasal catarrh and the results so far have been very promising.

Thomson, who is an international authority on the subject holds that the clinical evidence is increasingly convincing that this detoxication process will revolutionize the whole subject of vaccine treatment and preventive inoculation.

Differential Diagnostic Reaction.—

Irons (Jour. Inf. Dis., June 4, 1908) has called attention to the value of the reaction following the injection of gonococcus vaccine as a diagnostic point. He says: "A typical gonococcus reaction is characterized by a rise in temperature, often only slight; an increase in pain and tenderness in the affected joints, with occasionally some increase in swelling, and a variable degree of malaise. The symptoms follow the injection in from eight to twelve hours, and commonly last about twenty-four hours. Frequently there is a decided tenderness at the site of the injection, greater than occurs after the inoculation of the same dose of the

same preparation in normal subjects. Occasionally there is a marked redness and edema lasting from twenty-four to forty-eight hours. In a case of periurethral abscess of gonococcal origin without secondary infection, which was under surgical treatment with drainage, an injection of 500 million cocci was followed in eighteen hours by a moderate swelling and tenderness at the site of needle puncture, and also a marked increase in redness and tenderness about the wound. There was no coincident retention of pus or local secondary pus infection to account for the phenomenon, and the wound returned to its normal condition in twenty-four hours. There is usually a slight increase in leucocytosis in the first twenty-four hours after injection.

"The frequency with which these clinical phenomena occurred suggested the possibility of utilizing the reaction in the diagnosis of obscure cases of arthritis in which the gonococcus was the suspected cause. The effects of the injection of dead gonococci into patients not suffering from gonococcus infection were accordingly studied. Eight adults in whom there was no history or sign of gonococcus infection were given injections of 500 million dead gonococci. In none of these was there any local change other than that following an ordinary hypodermic puncture, and no fever or constitutional disturbance was observed. In a case of pyorrhea alveolaris with subsequent general infection and painful swelling over the extremities, there was no increase of fever or local symptoms following the injection. A case of gout with active joint involvement showed no local or general changes after a dose of 50 million. Leucocytes before in-

jection, 13,200; eighteen hours after injection, 13,000. Temperature was normal throughout. A case of articular rheumatism showed no reaction after a dose of 500 million. There was no increase in leucocytosis and the temperature chart showed no abnormal variations. A case of acute arthritis with pericarditis was thought possibly gonococcal in origin. There was no reaction after a dose of 500 million. Cultures from the blood and from a small amount of fluid aspirated from the knee remained sterile, and the prostatic fluid contained no gonococci. The subsequent course was typical of rheumatic fever. In 4 other cases of acute and subacute articular rheumatism there was no reaction after injections of 500 million cocci.

"In a number of suspected gonococcus cases the reaction was of value in making an early diagnosis. A case of monoarticular arthritis with effusion in the knee, in which gonorrheal infection was denied, was given an injection of 500 million. The evening temperature, which had previously reached only 100°, rose to 101.8°, and the joint pains increased. The knee was aspirated, and the gonococcus isolated in pure culture from the fluid. A case of chronic arthritis which had resisted all treatment was given an injection. A slight rise in temperature, with some increase in joint pains followed. The prostatic fluid was found to contain gonococci, and the subsequent course was that of gonococcus arthritis. A patient who had suffered from extensive gonococcus arthritis had been bedridden for one year. There was practically no motion in the knees. After an injection of 500 million, the temperature,

which for weeks had been normal, rose to 99.5°, and the patient complained of malaise and increased pain in the joints. A patient with aortic aneurism, who denied gonorrheal infection, had been selected for control by experimental inoculations. After an injection of 500 million cocci, the temperature, which had been uniformly normal, rose to 100° F. without any other apparent cause, returning to normal the next day, without any subsequent rise. The prostate was examined and found to be large and somewhat tender, and the secretion contained numbers of leucocytes with typical intracellular gonococci.

"The reliability of the clinical gonococcus reaction as a diagnostic procedure will be determined only after many tests. It has many points in common with the tuberculin reaction, and similarly too there may well be cases of gonococcus infection found which do not respond. It appears, however, to be well worth a trial. Should the reaction prove to be reliable, a valuable and much-needed aid will be at hand for the diagnosis of obscure joint, synovial, and periosteal diseases."

The results from the use of vaccine in gonococcus infections have been less uniformly satisfactory than in probably any other condition in which therapeutic inoculation has been given extensive trial.

Vaccine alone is insufficient to control or cure gonorrhea in the original sites of infection, such as the urethra, vagina, and conjunctiva, according to G. Cappelli (*Giorn. ital. delle mal. veneree e delle pelle*, June 12, 1916), but is of help in what may be called

secondary localizations of the gonococci, such as **epididymitis** and **arthritis**.

MacKinney (*Penna. Med. Jour.*, vol. xiv, pp. 284-288, 1910-1911) has carefully studied the effect of vaccines in 86 cases of gonorrhea and its complications. He says that small doses of from 5 to 50 million rarely cause any local or constitutional disturbance, and only with the dose increased to from 300 to 500 million was any disturbance noticed. Reactions following the administration of staphylococcic vaccine in chronic gonorrhea were more frequent than after gonococcic vaccine. The 86 cases treated included:—

Acute gonorrhea	23
Chronic gonorrhea	25
Epididymitis	26
Cowperitis	2
Arthritis	10
Tenosynovitis	3

In all 424 injections were given. The results are summarized with the statement that bacterial vaccines have not demonstrated their value in the treatment of acute or chronic gonorrhea or in the treatment of its acute complications. They have not, in the hands of this writer, produced a cure and have not proved their value as a useful adjunct to other treatment. In metastatic infections, gonorrheal arthritis, they have given good results in a few cases.

Shropshire (*Alabama Med. Jour.*, vol. xxiii, No. 11, p. 621, 1910) has treated a large series of cases including practically all the forms of gonococcal infection. The results in 500 cases are given; the total failures amounted to only 6.7 per cent. In acute conditions he gave the injections every third or fifth day; rarely

was it necessary to give more than six to eight injections. The initial dose was about $7\frac{1}{2}$ million, the next 15 million, the third 25 million; subsequent doses were increased to 40 and 50 million, if necessary. In chronic conditions the initial dose given was about 25 million and subsequent doses were increased about 25 million each time, the interval between doses being five to six or seven days. It has never been necessary to give more than 150 to 200 million gonococci at a single dose.

Buka (*Amer. Jour. Derma.*, vol. xv, pp. 72-73, 1911) is convinced that in both the acute and chronic forms of gonorrhea there is marked lessening of the dangers of complications in most cases; there is consequently a marked amelioration of the subjective symptoms. The annoying factor of long-standing gleet has been so satisfactorily overcome with the employment of vaccines that their use is invariably advocated when such a sequel is found to gonococcal infection.

Lumb (*British Medical Journal*, Oct. 6, 1917) treated 500 consecutive cases of acute gonorrhea with vaccines. The general effects of this treatment were as follows: 1. Mental relief at the rapid disappearance of the discharge. 2. Rapid disappearance of pain on micturition. 3. Rapid disappearance of pain on irrigation. 4. Exercise can be taken without delaying the cure. Of his 500 cases 222, or 44 per cent., had some form of complication. The average duration of the 278 uncomplicated cases was 35 days, or 5 weeks. The average stay of all complicated cases was 52 days. It has from time to time been suggested, though never with adequate proof, that vac-

cines are dangerous in the acute stage, and lead to complications. This was not the case. Of the 101 epididymitis cases 70 were present on admission, leaving 31 developed out of 430 cases, that is, 7 per cent. Of the 10 arthritis cases 8 were present on admission leaving 2 developed out of 490 cases, that is, less than 1 per cent.

The most remarkable feature of all is the exceptionally low percentage of relapses. Out of the 500 cases 2 only occurred during a period of 4 months after completion of the series. This gives a relapse rate of less than 1 per cent. It affords proof of the value of vaccines as a test of cure. At the present time everything possible has to be done to minimize the number of relapses of gonorrhea cases, and this system has been found, in actual practice, to be far in advance of any other; whilst the number of days under treatment compares favorably with any figures so far published.

Urethritis.—Read (*Amer. Med.*, Sept., 1911) has treated 6 cases of **acute gonorrhea** with autogenous and stock vaccine. The doses ranged from 10 to 100 million at three- to five-day intervals. In no case were the vaccines of benefit. The vaccines seemed to be of positive benefit in 1 case of **Cowperitis** after incision and evacuation of pus. There had been no improvement after two weeks' rest in bed. Seven chronic cases treated had been under observation for a year or more. In 5 of these which had resisted all treatment for many months the employment of vaccines in conjunction with some measures which had been used unsuccessfully formerly was followed by the disappearance of the disease within twelve to twenty weeks. Four of these "cured" cases have been

married over six months without signs of infection in themselves or wives.

Palmer (Med. Record, lxxix, 337, Feb. 25, 1911) has had favorable results from the use of stock vaccines in the treatment of **acute gonorrhea**. He has treated in all about 50 cases in a period extending over two years. The results have varied somewhat with the technique employed and the general results strongly favor the use of vaccine in these conditions. In earlier cases doses were used which later would have been considered too large. At first 5 minims of a vaccine containing 50 million bacteria per c.c. was the dose. This was usually followed by a slight reaction and an increase of the discharge succeeded in a day or two by a marked decrease. When the discharge was reduced to a few drops of a thin, watery secretion, it was found difficult to do more than this. Then the doses were increased as rapidly as possible, running up as high as 4 c.c. at a single injection. The writer now believes that such doses were much too large. In 1 case cited the last dose was 3 c.c. with no further decrease in the discharge. The injections were then stopped and the discharge ceased within two weeks of the last injection. At present he is using 2 minims of a 50 million vaccine with an interval of seven days. The doses are not increased except in occasional cases, and then only when it seems obvious that recovery is not to be obtained otherwise.

Livermore (Southern Med. Jour., vol. iv, No. 4, pp. 350-351, May, 1911) says that, as far as a case of **very acute or chronic anterior or posterior**

gonorrhea is concerned, his experience has convinced him that gonococvic vaccine as a cure is *absolutely worthless*. He has used it in all doses and at variable intervals, and in no case could he effect a cure or show a modicum of improvement. On the other hand, some of the complications of both acute and chronic gonorrhea sometimes yield promptly and satisfactorily to the administration of the vaccine. The complications in which the vaccine has given the *best results* in his hands are **epididymo-orchitis, arthritis, and prostatitis**. In epididymo-orchitis the initial dose is usually 25 million and increased 25 to 50 million at each subsequent injection. The interval between injections should not be less than four days, as a transient increase in the pain in epididymo-orchitis and arthritis has been noted when the injections have been given oftener than every four days.

Cunningham (Trans. Amer. Asso. of G.-U. Surg., vol. v, pp. 293, 324, 1910) reports 4 cases of chronic prostatitis and seminal vesiculitis treated with vaccines which were not benefited.

M. Cappelli (Giornal Ital. delle Mal. Ven. e della Pelle, Feb. 12, 1917) reports 84 cases of **acute and subacute gonorrheal urethritis** treated solely by vaccines with 64 cures, or 76 per cent.; 32 cases of **chronic urethritis** with 31 cures; 27 cases of **epididymitis** with 26 cures; and 5 cases of **gonorrheal rheumatism**, all cured. Failures are attributed to the fact that a vaccine is not stable in composition. Complete rest in bed is emphasized.

Mixed Infections.—In the treatment of **chronic urethritis and pros-**

tatit it must be remembered that mixed infections are the rule. The chief rôle of the gonococcus seems to be to make the soil suitable for the growth of other bacteria. The other bacteria commonly found are streptococci, staphylococci, colon bacilli, and diphtheroids. A mixed vaccine should be used when the condition is of more than a few weeks' standing.

Buka (*Amer. Jour. Derma.*, pp. 74-82, Feb., 1910) reports a case of chronic urethral discharge which microscopic examination demonstrated was due to mixed gonococcic and streptococcic infection. The discharge, which was profuse, thin, and glairy, had continued for over a year and did not yield to treatment. The case presented a long prepuce, which called for circumcision. The patient was put on the regular internal and local treatment for gonorrhea, and an initial dose of 100 million each stock gonococcic and streptococcic vaccine was given. This dose was repeated three days later, but six other injections were of gonococcic vaccine alone. After the seventh injection (the fifth of gonococci alone), the discharge had completely disappeared. A week after the eighth and last dose, the prepuce was circumcised and the wound healed by primary intention. No complications developed, and recovery was considered complete. The intervals between doses were three, three, three, four, two, four, and three days.

Eyre and Stewart (*The Lancet*, pp. 76-81, July 10, 1909) says that: "A chronic urethral inflammation is not, as a rule, a simple infection. The ravages of the gonococcus over a long period leave the superficial and deeper

layers of the urethral mucous membrane in a condition little calculated to resist the invasion of other organisms or to encompass the destruction of the gonococci themselves. It is not surprising to find that the presence of the gonococcus alone, in cases of chronic urethritis or cervicitis of nine months' duration or longer, is the exception rather than the rule."

Rush (*Gulf States Jour. of Med. and Surg. and Mobile Med. and Surg. Jour.*, Oct., 1909) reports a case of chronic gonorrhea in which there was a history of several attacks of acute gonorrhea, one of these attacks having been accompanied by prostatitis, and epididymitis. The patient suffered from an aching, dull sensation in prostate, and in damp weather had rheumatic pains in elbows and shoulders. For ten days prior to coming under treatment he had profuse urethral discharge, burning sensation on micturition, pain in left testicle, and pain in elbows, ankles, and wrists. Microscopic examination showed mixed infection of gonococci and staphylococci in the urine as well as in the heavy, yellowish discharge coming from the meatus. Gonococci were found in the thickish brown pus, which exuded from the urethra during local treatment. Injections of 50 million stock gonococcic and 100 million stock staphylococcic vaccines were given for a period of three months, in conjunction with other treatment. The gonococcic vaccine was injected every third day, and the staphylococci every fifth day. Rush says: "The patient has gained in weight, feels better than in five years, has no rheumatic pains and no morning drop, nor shreds in urine."

The case was discharged as cured at the end of the third month of treatment, and two thorough examinations proved negative.

Epididymitis.—Friedländer and Reiter (*Derma. Zeits.*, 18, pp. 75-77, 1911) have treated 125 cases of acute, subacute, and chronic gonorrheal epididymitis with polyvalent vaccines according to Wright's directions (Reiter's vaccine was used, prepared according to Wright). Doses began with 0.2 c.c. and if there was no rise in temperature they were increased at intervals of two or three days—0.4, 0.6, 0.8, 1.0 c.c. No marked systemic disturbances were noted; occasionally some restlessness, slight perspiration, and a little headache were noticed. There was never albumin in the urine. In only 1 of the 25 cases an erythema the size of small plate developed. The injections themselves caused no pain, but from twelve to eighteen or twenty-four hours after injection the affected organ became acutely red, the skin shiny, and there was a slight increase in the painfulness and swelling of the inflamed area. The authors considered these findings as a "local vaccination." This they consider especially important. Within several days resorption of the infiltration occurred. The authors have never had a case of tuberculous epididymitis upon which gonococcus infection supervened, but they feel certain that vaccine treatment clears up epididymitis more quickly than any other treatment.

In conclusion they state that vaccine treatment gives exceptionally good results in acute epididymitis and satisfactory results in subacute gonorrheal follicular prostatitis, in which case

the course of disease is at least always shortened. If this is supported by other therapeutic measures, results are always good, but in cases of subacute anterior and posterior urethritis, in gonorrheal urethrocystitis, the vaccine treatment does as yet not compare favorably with the silver injections.

Gonococcic Arthritis.—According to Murrell (*Practitioner*, 523, vol. lxxxviii, 1, pp. 34-45, Jan., 1912): "The popular term 'gonorrheal rheumatism' has been gradually superseded by 'gonorrheal arthritis,' or, to be more precise, by 'gonococcic arthritis.' 'Urethral arthritis' has been suggested, but has met with little favor. All these names are open to objection, chiefly on the grounds that the arthritis is commonly a synovitis, and that in the chronic forms the organism is not the gonococcus but some later development in the bacterial world. The joint changes are indications of a general gonococcic invasion characterized not only by arthritis but by iritis, scleritis, endocarditis, pericarditis, peritonitis, localized pleurisy, metritis, salpingitis, meningitis, and inflammation of the fibrous tissues generally. This list is by no means complete, and one of my students enumerated forty complications of gonococcic urethritis of many of which he has had practical experience."

After discussing the usual methods of treatment, he concludes: "The only effective method of treating gonococcic arthritis is by vaccine therapy, and that with certain reservations. The ordinary stock gonococcic vaccine is of very little value. I recently saw a man who for many weeks had been treated on these lines without benefit, the explanation being that his gonococci had long

since disappeared and had been replaced by a diphtheroid bacillus, which was the cause of the mischief. Somewhat better results are obtained by vaccine prepared from a recent alien gonococcic urethritis, but even that leaves much to be desired. These vaccines are usually composed of several strains, but I am not in favor of this particular form of polypharmacy. As far as possible I discard alien vaccines and use only autovaccines, for the antidote prepared from the patient himself is of infinitely more value than a remedy obtained from an unknown source.

"In some cases I have used large doses, even up to 500 million, every three or four days. It is said that the dose for the urethritis should be 75 million, for the iritis 250 million, and for the arthritis 500 million, but I do not endorse the action of the medical man who gave an initial dose of 825 million. I am in accord with Hartwell, who finds that autogenous vaccines are valuable in all stages of gonococcic arthritis except when ankylosis has occurred. As a detail many patients have an objection to being inoculated with gonococci obtained from people respecting whose moral character they have no information. I have treated many cases with alien vaccines, the doses of the injections being gradually increased from 5 to 200 million. The number of injections given ranged from 8 to 25, but in a chronic case this is inadequate. In 3 recent cases the number of days in the hospital was 67, 76, and 114, respectively. Better results are obtained by autotherapeutical inoculations; the actual organism causing the arthritis is isolated and the results are naturally more satisfactory. In a case of gonococcic arthritis of four months' dura-

tion treated with an autovaccine, the organism being a diphtheroid bacillus obtained from the urethra, the first injection of 5 million was given on June 1st and was gradually increased to 50 million. By the end of July 20 injections had been given and the condition was cured.

"Valuable as are inoculations they are not everything, and there is still scope for the ministrations of the surgeon. I recently saw a case of gonococcic arthritis in which heterovaccines and autovaccines carried out for a long period and with the most careful attention to detail failed to effect an improvement. A surgeon was requisitioned, who by dilation of the urethra under an anesthetic removed the focus of infection, allowing the antidotal treatment to exert its influence."

Twenty cases of chronic arthritis of various types, all tentatively diagnosed as due to streptococcal infection, and treated with streptococcic vaccines are reported by Jones (*Brit. Med. Jour.*, May 17, 1913). The results in at least 8 cases indicated that streptococcal infection is concerned in chronic arthritis, though fluid removed by puncture and blood-cultures was sterile. The vaccines used were of streptococci obtained either from the mouth (in cases of oral sepsis), from the urine, or from the feces.

Chronic gonorrheal arthritis is due to a mixed infection with the gonococcus and staphylococcus, according to Hughes (*Brit. Med. Jour.*, 2737, 1267, 1913), both of which can be cultivated from the interior of the urethra. An autogenous vaccine containing from 100,000,000 gonococci and 150,000,000 staphylococci up to 500,000,000 of the former and 1,000,000,000 of the latter,

should be used, and after the second dose the chronic gleet treated locally. The author has had very good results with this treatment, though a complete cure often requires weeks or months.

In 7 out of 10 cases of joint and tendon-sheath infection treated by Read (*Amer. Med.*, No. 8, N. S., vol. vi, pp. 494-499, Sept., 1911) the results were direct and positive. Even twenty-four hours after the first inoculation there was distinct improvement. The writer concluded that stock vaccines are seemingly as efficient as autogenous vaccines, but when these fail autogenous should be tried. Vaccines in acute gonorrhea are of no value. In one subacute case they were seemingly of benefit. In obstinate chronic cases they are of use in conjunction with other measures. In gonorrheal rheumatic conditions they are of positive worth; often their results are directly brilliant and no case of gonorrhea with complication should be denied the early employment of this remedy.

Hartwell (*Ann. of Surg.*, Nov., 1909) reviews 51 cases of gonorrheal arthritis treated with gonococcus vaccines. These were cases in the Massachusetts General Hospital. Vaccines killed by heating to 60° C. for one hour were compared with vaccines prepared without the use of heat. No striking differences were noted. The patients with acute conditions were inoculated more frequently and received smaller amounts than the more chronic ones. They received doses ranging from 10 to 25 million and progression was made up to 100 million. The doses were given at intervals of from two to four days in the acute cases, and every five days to a week in the more chronic ones. In the chronic conditions the

amount was often pushed up to 500 to 600 million. Thirty-one or more than half the cases were seen when the acute inflammation had subsided. They came for treatment at periods varying from one month to a year after the acute attack. The joints were swollen, stiff, and painful when used. In 27 of these cases the result of treatment was successful and the patients were discharged with complete functioning joints without disability. They have all reported at intervals of from a month to a year after their discharge, and in all the perfect joint function has been maintained. Twenty of the cases were seen a few days after the onset of their joint symptoms. Eleven of these were simple hydrops; all were polyarticular except one. Vaccines diminished their pain and hastened resolution. Only 3 of the patients did not recover with perfect results. In 9 of the acute cases the process in the joints had become purulent or seropurulent, with infiltration of the periarticular structures. They were all monoarticular; 6 of these recovered with joints which were capable of complete free motion. In 2 of them which were both suppurations in the knee-joint some slight thickening remained as late as five months after their discharge, but these afford no obstacle to joint function. Three of these 9 cases had more or less joint disability after their discharge.

In arthritis the initial dose given by Livermore (*Southern Med. Jour.*, vol. iv, No. 4, pp. 350-351, May, 1911) is usually 50 million and an increase of 50 million each time. Gratifying results have been obtained in this distressing condition. In the treatment of gonorrhea in women he has several

times noted cases that seemed to be benefited by the vaccine, although this may have been a coincidence. In his experience gonococcus vaccine has not proven a prophylactic against the occurrence of complications, as he has often seen them develop after the vaccine has been used.

Cunningham (Trans. Amer. Asso. of G.-U. Surg., vol. v, pp. 293-324, 1910) has treated 29 patients suffering with various forms of gonorrheal infection. He used both stock and autogenous vaccines. The dosage in acute febrile cases varied from $2\frac{1}{2}$ to 10 million and in chronic cases from 10 to 75 million. An injection of 100 million was sometimes given for diagnosis. In the patients with gonorrheal rheumatism the vaccines did not appear to shorten the febrile period, but the patients were more comfortable and may have had less pain in the joints when small doses of vaccine were used. No joints that were not already involved became involved later. In the postfebrile cases almost immediate alleviation of the symptoms after the first dose or two was generally noted. Massage has been of value in several cases where stiffness persisted. Those cases having a urethral discharge have either cleared up or improved considerably during treatment; whether or not this was due to the vaccines cannot be said, as local treatment was always given.

Eyre and Stewart (The Lancet, pp. 76-81, July 10, 1909) report that "the effect of vaccines was practically identical in all cases. In from twelve to twenty-four hours after the administration of 5 to 10 million the affected joints were subjectively more

painful, and in many cases distinctly more swollen, red, and tender, and movements more limited. These symptoms correspond with the negative phase. In from thirty-six to forty-eight hours symptoms cleared up, pain and tenderness passed off, and movements became much more free." Some of these cases were treated with stock vaccines and some with autogenous preparations.

Maini (La Presse médicale, p. 40, January 16, 1909) found that in doses of less than 1 million the vaccine was ineffective, but that when given in this dose it caused a marked decrease in the painfulness of the joints. Immediately after the injections there was a temporary increase in the pain, lasting only a few hours; and this reaction he considers a valuable means of distinguishing between gonorrheal arthritis and that due to other causes.

Jack (The Lancet, p. 575, Feb. 26, 1910) reported 4 cases of gonorrheal arthritis successfully treated.

In 443 cases of gonorrheal arthritis Chiari (Centralbl. f. d. Grenzgeb. d. Med. u. Chir., Sept., 1914) applied vaccine therapy with autogenous or commercial vaccine. Only 41 cases were uninfluenced; 32 patients were improved and 367 cured.

Robinson (Amer. Jour. of Urol., pp. 110-112, March, 1909) reports a case of gonorrheal arthritis treated for a week with very large doses of calx sulphurata and arsenic sulphide, and inunctions of ung. Credé, but the results were practically nil. He then started to use gonococcus vaccine, and after the eighth injection the patient was able to walk freely, stating that in three years he had not been so free from pain. The swelling

of the knees and around the ankles was almost completely gone. Three injections of 25 million each and five of 50 million each were given. No other remedies whatsoever were employed.

Ebright (Amer. Jour. Urol., pp. 110-112, Mar., 1909) reports a case of gonorrheal arthritis successfully treated with gonococcic vaccine. He says: "The action of dead cultures of gonococci in cases of arthritis in the relief of symptoms, especially pain, is often very prompt, sometimes dramatically so, as the following instance illustrates: A teamster, 31 years old, came to our wards having had urethritis one month and very severe pain in both knees for four days. Examination showed that both knee-joints contained much fluid, were very painful and so exquisitely tender that the slightest jar caused the patient to wince pitifully. One knee-joint was aspirated and 40 c.c. of turbid fluid were withdrawn, in which gonococci were easily demonstrable. The next morning the relief following the removal of the fluid had gone, the aspirated joint was as tense as before, both knees being greatly distended with fluid and causing as much suffering as ever. Salicylates in large doses had no effect and were discontinued. Ten million dead gonococci were given subcutaneously in the arm, and the interne was instructed to withdraw the fluid from both knee-joints the following morning if the condition was no better. This, however, proved to be unnecessary. By the end of twenty-four hours the clinical picture was entirely changed. The pain and tenderness had gone, and the joints, instead of

being hot, hard, and tense, were cool and relaxed, the fluid having greatly receded. By the end of six days the fluid was still demonstrable, but the patient was walking about the ward. He was given 10 million more dead gonococci, and within a few days no exudation in the joints could be detected. Recovery was considered complete in sixteen days after the first injection."

Berghausen (Lancet-Clinic, pp. 55-61, Jan. 16, 1909) reports 3 cases of gonorrheal arthritis treated with autogenous vaccine. The first case was given five injections at intervals of about a week, the doses being respectively 100, 200, 350, 420, and 420 million. The second case received five injections of 60, 200, 200, 350, and 350 million, respectively. The intervals were four, six, seven, and seven days. The third case was given two injections (20 million each) of a stock vaccine, two days apart, without improvement. A month later, 60 million of an autogenous vaccine was given, followed within three days by relief from pain. A dose of 200 million was then given, followed a week later by 360 million, and after another week by 440 million.

Pyosalpinx.—Some gratifying results have been obtained by Palmer (Med. Record, lxxix, 337, 1911) in **gonorrheal pyosalpinx**, both in acute cases and in acute exacerbations. Four patients have been treated, but since all of them were satisfied with the improvement they made and withdrew from further treatment before all signs of the disease were gone the results can only be recorded as symptomatic cures. Even this result was very gratifying, as all of them would

have required hysterectomy if vaccines had not been used. The doses given one of these patients were 4 minims of the vaccine (1 c.c. = 50 million) administered every other day for a week and then twice a week. At the time she refused further treatment the tubes were two small, hard strings; leucorrhea was slight, and showed no gonococci. Favorable results were also obtained in 2 cases of gonorrheal rheumatism and in 1 of gonorrheal conjunctivitis.

Vulvovaginitis.—Among the earliest reports of work done in this country with gonococcus vaccine was that by Butler and Long (*Jour. Amer. Med. Assoc.*, pp. 744-747, Mar. 7, 1908), and later by Butler (*Interstate Med. Jour.*, pp. 510-514, July, 1910). Butler and Long state that they varied the dosage in different cases and that no positive amount could be advised; but that the immunizing response to a given dose must be investigated in each case as indicated by the index, doses either too large or too small causing little or no response.

Inoculations were usually repeated every five or six days. Dr. Butler, in a further report of the work in continuation of that done by himself and Dr. Long says: "We found that cases got along well, as indicated by the index and clinical improvement, on doses between 5 and 10 million; and we believe that an average dose for beginning treatment was from 10 to 25 million; and that this dose might be increased if desired, but that we obtained our best results with doses of from 5 to 50 million. . . . We decided that a patient should be inoculated at least every fifth day during treatment."

Their first report covers 12 cases. In 4 of these cases the clinical appearance of gonorrhea disappeared in from ten to twenty-one days, in 5 cases a longer period of treatment was required, and in 3 particularly stubborn cases the discharge finally ceased. Their second report covers 25 cases—12 acute and 13 chronic. Seventy-five per cent. of the acute recovered and the other 25 per cent. showed improvement; 85 per cent. of the chronic cases recovered.

Hess (*Amer. Jour. Dis. of Child.*, Nov., 1916) urges that the cervix is usually involved, and that in chronic cases the vagina may show no signs of inflammation. Numerous pus cells without bacteria in smears made from the cervix indicate almost invariably a gonorrheal infection. In the newborn, however, the invasion of the vagina by saprophytic bacteria may cause a purulent discharge which is hardly pathologic. Gonorrheal vaginitis or cervicitis is not to be regarded as an institutional disease, as it occurs in a considerable proportion of infants living in the crowded tenements of the city.

In child-caring institutions the greatest obstacle to controlling the disease is the difficulty of recognizing latent cases. By means of provocative inoculations of gonococcus vaccine in doses of 100-400 million, the writer was able to convert the concealed carrier into an open case, and thus discover many which had escaped detection. Vaccinations have also some prophylactic value.

Alice Hamilton (*Jour. Inf. Dis.*, Mar. 30, 1908), refers to 7 chronic cases in which local treatment had been given a fair trial, and failed to bring about improvement. "One of

our 7 (Case II) proved refractory to inoculations also, and she evidently represents that very obstinate form of gonorrhea in childhood which is most dangerous because so seldom recognized. The other 6 cases improved decidedly under the injections of killed gonococci, as is shown by the fact that, while the average duration of vaginal discharge prior to treatment (in the 5 cases in which this could be ascertained) was a little less than four months, the average duration after treatment was not quite three weeks. It is not claimed that a permanent cure was effected in any of these children. The experience of all who have carefully studied this disease is that recurrences are to be expected after apparent recovery. It is only claimed that the disease can at least be temporarily controlled by raising the opsonic index to the gonococcus through the injection of dead gonococci.

"Even if the progress under inoculations were no more rapid than that caused by the usual methods of local treatment, there would still be decided advantages in its favor. Everyone recognizes the drawbacks to local treatment in babies and little girls; a treatment almost impossible in any place but a hospital, and not free from risk even there. Bumm stated that he had seen all the symptoms of an acute peritonitis follow the administration of a vaginal douche in a little girl, and while such an event can hardly be regarded as anything but most exceptional, it must be admitted that there is some risk of driving the infection up into the cavity of the uterus. Aside from this, there is the less serious risk of pro-

ducing slight mechanical injuries and of inducing the habit of masturbation, both of which would result in prolonging the course of the disease. In our cases douching was suspended soon after the inoculations were begun, and it was evident that not only was the progress of the case not retarded thereby, but in some instances it was hastened. Three little girls had been incorrigible masturbators as long as they were given vaginal douches, but when the latter were abandoned they seemed to have no further temptation to this habit—a change which certainly contributed to their recovery.

"In 7 of the acute cases and in 5 of the chronic cases the opsonic index was followed, and the injections of dead gonococci were given according to the index. The interval between injections was at first from five to seven days; then, as we noticed that a second rise in the index sometimes occurred if the injections did not follow each other too rapidly, we lengthened the interval to eight or nine days. Those children whose indices were not studied were injected regularly according to this rule.

"In our experience it is advantageous to follow the index while giving inoculations, although it is not essential. The index does serve as a valuable guide in determining the amount and the time of injections. However, when this is not possible the treatment can still be carried out with success."

Conjunctivitis.—Ohlmacher (Jour. Amer. Med. Assoc., vol. xlviii, p. 571) has treated 3 cases of gonorrheal conjunctivitis. Two of them were cured while 1 was improved. Miller (Glas-

gow Med. Jour., p. 356, 1908) has had favorable results in the treatment of 2 cases. Eyre believes that unless the vaccine is given with extreme care and the injections are controlled by the opsonic index definite harm may ensue. He mentions a case treated with gonococcus vaccine in which an injection was given at the wrong time. Practically the whole cornea was lost.

Bryan (Brit. Med. Jour., vol. i, p. 663, Mar. 23, 1912) says: "Acute gonococcal conjunctivitis is a disease of grave prognosis, and here vaccine is of great value. Of 2 severe cases which I have treated, in 1 a cure was obtained in ten days; in the other no apparent benefit resulted. I have treated 3 cases of gonococcal ophthalmia in newborn infants with doses of $\frac{1}{2}$ to 1 million of vaccine: the disease became cured in each case without infection of the cornea."

Rubbrecht (Bull. de la Société Belge d'Ophthal., 27, p. 82, 1909) reports a case of systemic gonorrhea with conjunctivitis and keratitis in which three doses of gonococcus vaccine (5, $7\frac{1}{2}$, and 10 million) were given with excellent results. There was no corneal ulceration, but when the conjunctivitis was well three attacks of peripheral keratitis occurred, extending over a period of one month. Weeks (Trans. Amer. Ophthal. Soc., vol. xii, part ii, p. 598, 1910) recommends doses of $2\frac{1}{2}$ to 50 million of polyvalent gonococcus vaccine, but has found it of little value in acute infection. Bryan (*loc. cit.*) thinks he used too large doses and produced negative phases, from which there is not time for recovery in acute cases. McKee has treated with vaccine 3

cases of metastatic gonococcal inflammation of the conjunctiva with success.

Iritis.—Eyre and Stewart (The Lancet, pp. 76-81, July 10, 1909) report 4 cases of gonorrheal iritis, giving detailed accounts owing to "the importance of this uncommon complication."

Case I.—The patient had suffered from gleet for ten months in this, his third attack of gonorrhea. The right pupil was dilated (atropine) and irregular; some chemosis; conjunctiva very injected and lachrymose; no purulent discharge and the eye extremely painful. By the second injection the pain had almost disappeared from the eye, which in all ways appeared better. Ten days after the second injection the patient said that the eye had been free from pain for a week for the first time for nearly six months. The earlier injections had the usual effect on the urethral discharge, which eventually disappeared. Treatment was carried out for two and a half months, and at the expiration of this time the iritis was cured and the sight was perfect.

Case II.—Present attack of gonorrhea contracted five months ago. Three recurrent attacks of conjunctivitis (both eyes), but no pain or loss of sight. Present attack left eye only, starting one month previously; great pain, congestion, and loss of sight. Conjunctiva very injected (ciliary); iris muddy; no reaction to light; pupil irregular; cornea hazy, with deposits in anterior chamber. Pain on admission very bad, and getting worse. Pain relieved within forty-eight hours of first injection; gone in four days; sight returning; eye steadily improv-

ing; patient feels better in general health two or three days after each injection. No relief of pain prior to vaccine, while under treatment by fomentations and atropine.

Case III.—Present attack of gonorrhea contracted one month before commencement of iritis. Lids injected and swollen, mucopurulent discharge, but gonococci absent; conjunctiva injected; chemosis; cornea healthy. Eleven days after admission, arthritis of knee and elbow, Arthritis well, and patient discharged cured in a month from first vaccine inoculation.

Case IV.—Patient admitted with "cold" in the right eye; marked conjunctival injection; discharge; very severe pain, especially at night; cornea cloudy; pupils dilated, iris dirty colored; condition getting worse. One month from date of admission, eye greatly improved; no discharge; iris clear; no conjunctivitis; cornea clear. Pain relieved after first injection; cured after the second.

Reber and Lawrence (Ophthal. Rec., Jan., 1915) have recorded 3 cases of iritis in which the complement-fixation test established an old latent gonococemia, which yielded promptly to bacterin treatment. Gonorrheal iritis is more frequent than rheumatic.

Accessory methods of treatment are of much importance in gonococcus infections and the usual methods of treatment are not contraindicated. MacGowan (Calif. State Jour. of Med., pp. 83-84, March, 1910) says: "When it was first known that a vaccine could be prepared from a gonococcus its advent was hailed with fervor, and the long-looked-for quick cure was believed by many to have

been found. We have treated quite a number of cases of gonorrhea, a few with vaccine alone, but commonly and always now with the remedies and measures usually employed in this disease. We still treat all granular patches in the urethra by direct applications through the endoscope; dilate any strictures that may be present; massage the diseased prostate and vesicles; use urethral and vesical irrigations and instillations and general tonics. But we do not waste time and money by administering balsamics, either plain or in nauseous mixtures. Vaccine treatment is to be added to the ordinary approved methods as an adjunct, but is not to be depended upon as a specific method of curing the disease in question."

Ballenger (N. Y. Med. Jour., pp. 21-22, July 3, 1909) says: "Stale pus and retained body fluids are poor in antibacterial substances, and when possible should be replaced by fresh secretions rich in such substances. . . . Hot urethral irrigations (1000:5000 potassium permanganate solution with 1 dram sodium chloride and 2 drams boric acid to 2 quarts) should be administered daily until the purulent discharge ceases. . . . Hot rectal douches appear to be of use in the treatment of prostatitis, and probably produce their good effects by promoting a freer flow of blood through the inflamed parts."

Allen ("Vaccine Therapy and Oponic Treatment," 3d ed., pp. 132-133) says: "The topical application of antiseptics to infected glands and lacunæ, and flushing the canal with weak lotions, still remain the first es-

entials to success; but they may find in vaccine treatment a most useful adjuvant. . . . The necessity of preventing access of other pathogenic organisms can hardly be too strongly insisted on, and is best secured by means of a roll of cyanide of mercury gauze placed over the extremity of the penis. Flushing of the urethra with very weak antiseptic lotions by means of an irrigator twice daily at the appropriate period in the attack will greatly assist the cure."

Eyre and Stewart (The Lancet, pp. 76-81, July 10, 1909) say, in regard to "other therapeutic agents" in acute gonorrhea: "In addition to the vaccine, very dilute solutions of potassium permanganate were employed in a few cases of urethritis and vaginitis. . . . Painful joints were wrapped in cotton-wool, and in many cases a mixture of some sort, generally citrate of potash and sulphate of magnesia or infusion of buchu, was administered by the mouth. Finally, in a few instances of arthritis, massage and radiant-heat baths were employed toward the end of treatment, in order to increase the mobility of the joint."

Ulrich (St. Paul Med. Jour., pp. 361-372, July, 1909) advocates "rest; massage at the right time, either externally along the urethral tract or internally by sounds and irrigation."

Jamieson (Therap. Gaz., May 15, 1910), in referring to the necessity of accessory treatment when using gonococcus vaccine, states: "Many observers have given the vaccine a trial by employing it alone in the cases they have treated. These men have given discouraging, or at least lukewarm, reports of its efficacy.

They did not use other measures which would tend to bring the antibacterial properties of the blood-serum in contact with the infected tissues."

STAPHYLOCOCCUS.

The staphylococci are the most common pyogenic organisms. It has been the tradition in textbooks from the early days to consider as pyogenic staphylococci the *Staphylococcus pyogenes aureus*, *Staphylococcus pyogenes albus*, and *Staphylococcus pyogenes citreus*. The *Staphylococcus pyogenes citreus*, however, is so rare that it scarcely ever need be considered as a producer of pus. The majority of those who have encountered organisms which would answer the description have been in considerable doubt as to whether it was not really either an aureus or one of the non-pyogenic cocci commonly found in water and in the air.

The pyogenic staphylococci may be isolated from the skin, frequently from the nose and throat, and from the feces of animals, and are ubiquitous in nature. In abscesses Allen found the staphylococcus alone in 67 out of 73 cases. One had streptococcus alone and 5 a mixture of staphylococcus and streptococcus. Abscesses in various parts of the body, especially those superficially located, are practically always caused by the staphylococcus. It goes without saying that ulcers are either caused by the staphylococcus or are infected by it as a secondary invader. Ulcers are less frequently the result of a pure infection because there is every opportunity for other organisms to enter. Allen found a pure staphylococcus in only 16 out of 39 cases. A pure strep-

tococcus infection was found in 5 and a mixture of staphylococci and streptococci in 18.

The *Staphylococcus albus* is the common organism associated with the acne bacillus, especially the pustular variety. The *Staphylococcus aureus* is found less often.

Diseases of the bone are usually caused by tubercle infections. When the condition is suppurative, however, the streptococcus is the most common associated organism. Ulcer of the endocardium, while more frequently the result of the growth of the streptococcus, may be caused by the staphylococcus. Pleurisy, peritonitis, and meningitis may also be mentioned as sometimes due to the pyogenic staphylococci. Among the more chronic conditions caused by them may be mentioned sycosis.

From the preantiseptic days in surgery we have inherited the ability to make a diagnosis with a fair degree of accuracy from observation of the character of the pus. If it is of a creamy yellow color one may conclude that the *Staphylococcus pyogenes aureus* is the offending organism, or is one of the chief among the offenders if it is a mixed infection. Pus of a whiter color, which used to be called "laudable pus," may contain *Staphylococcus aureus*, but probably contains the *Staphylococcus albus*.

Treatment of boils and carbuncles by staphylococcus vaccines is rapidly becoming the routine procedure, and there seems no reason why the use of vaccines in these conditions should not be practically universal. The literature already contains a great number of reports and the results recorded have been uniformly good.

Dosage.—If the patient is very toxic or the disease extensive the doses should be small (50 million) and repeated frequently, even as often as every day or every third or fourth day. If the carbuncle is of only ordinary size and the patient is otherwise in good health, the doses may be much larger, from 250 million up to 1000 million. The best plan is always to inject a small initial dose. Solari (La Semana medica, July, 1917) injected from 10 to 60 c.c. in 24 hours in six cases with excellent results.

Chronic furunculosis is liable to recur, and for this reason it has been found advisable to give injections at intervals of two weeks to a month for about six months after all symptoms of the trouble have disappeared.

In those patients suffering from an abscess which contains pus at a point very deep seated, it is a question for consideration whether it is wise to attempt to abort such an abscess by the inoculation of small doses or attempt to induce a negative phase by a large dose, encouraging the abscess to break down. The question must be decided on clinical indications; if there is much pus present it will be absorbed only very slowly and a painful lesion will be present for a considerable period. If it is possible, good results are likely to follow the aspiration of the pus by means of an ordinary syringe. In staphylococcus infections a stock vaccine is nearly always successful.

Wright has repeatedly called attention to the value of sodium citrate compresses as an aid to the evacuation of the pus in order to bring a flow of fresh lymph to the focus of infection. The abscess is pricked with a sterile needle or with a small knife, and com-

presses soaked in a hot solution containing 1.5 per cent. sodium citrate and 5 per cent. sodium chloride are applied. The hypertonic solution tends to attract the fluids, and much of the broken-down tissue and infectious fluid will be found to come away on the gauze.

In the treatment of **ulcers** compresses containing sodium chloride and citrate are especially valuable. The dosage for ulcers is about the same as for carbuncles. It is always advisable to have a bacteriological diagnosis made in the case of ulcers. They are more likely to be the result of mixed infections, as stated above, and if so a mixed vaccine should always be used. When it is impossible or not practical to have such a diagnosis made immediately, it is generally safer to conclude, for temporary treatment, that the staphylococcus and streptococcus are present and to use a vaccine containing these organisms.

The initial dose of the mixed vaccine may be estimated at 50 million staphylococci and 10 million streptococci.

Disease.	Number of cases.	Cured.	Improved.	Not benefited.
Cancrum oris ..	1	1		
Prostatitis	6	6		
Adenitis	3	2	1
Salpingitis	2	2		
Acne	139	74	48	7
Carbuncles	24	23	1	
Furunculosis	140	125	12	3
Sycosis	28	13	10	4
Atrophic rhinitis.	10	10	
Sinusitis	3	3	
Otitis media	34	19	11	4
Local infections.	114	39	55	20
Postoperative infections	39	28	7	4
Totals	543	332	157	45*

*Sic.

Sinuses and fistulas, especially **fistula in ano**, are rendered more difficult to treat by reason of their peculiar pathology. The tract is the seat of infection throughout its whole course, and if it is at all chronic it is composed of a thick layer of granulation tissue, the so-called pyogenic membrane. It is generally advisable to administer several doses of vaccine before removing this pyogenic membrane by surgical treatment. This is done that the opsonic index may be high at the time of operation and give the patient the best chance to recover.

Staphylococcus Vaccine.—Stoner (Maryland Med. Jour., vol. liv, pp. 153-157, May, 1911) gives the collected results obtained by the use of bacterial vaccines in a large number of staphylococcic conditions. These results summarized as in opposite column.

Carmalt Jones ("Introduction to Therapeutic Inoculation," MacMillan, London, 1911) reports 120 cases treated with staphylococcus vaccine. The following table will show results:—

Disease.	Number of cases.	Cured.	Improved.	Unchanged.
Abscess	96	67	23	6
Impetigo	10	4	4	2
Sycosis	8	3	4	1
Ulcer	3	3	
Acne	2	2	
Cystitis	1	1	
Totals	120	74	37	9

MacGowan (Calif. State Jour. Med., viii, 82, 1910) has reported the treatment of 2 cases of **chronic cystitis** with staphylococcus vaccine. In both small doses were used (80 million), the intervals between being only two days. In 1 case four such doses were

necessary, and in the other only two to clean up the general condition, reduce temperature, and relieve the septic condition.

MacDonald (Archives of Pediatrics, vol. xxviii, pp. 772-773, 1911) treated 28 children, varying in age from 2 months to 3 years, suffering with **furunculosis**. The *Staphylococcus aureus* and *albus* were the causative organisms in all cases. The average initial dose was 25 million staphylococci. Some received as high as 150 million without untoward results. In 3 cases there was slight redness and swelling at the point of inoculation; but this subsided in two or three days. One most interesting case is reported in some detail. A girl 1 year old, after a somewhat protracted attack of enteritis, became covered with small pustules about the size of a pea. Local treatment by the usual means of evacuating the pus and internal administration of calcium sulphide apparently had no effect, as the pustules increased in size and number. At the time vaccine treatment was started the entire body was covered with furuncles about the size of a small hickory nut. The general condition of the child was poor, temperature 102° and respiration shallow and rapid, probably due to septic anemia. The infecting organism was found to be *Staphylococcus aureus*, and a vaccine was made. The first dose was 25 million. Seven days later the furuncles that had been opened had stopped discharging and were beginning to heal; the breathing had become better and the child's temperature was normal. After four more injections, seven days apart, the last of which was 100 million dead staphylococci, all lesions had disappeared, res-

piration was normal, and recovery was uneventful. Beeman has also treated successfully with bacterial vaccines a **chronic blood infection** caused by the *Staphylococcus aureus*.

During the preparation of the autogenous vaccine, which takes 2 days, H. Beattie Brown (Annals of Otol., Rhin. and Laryn., Sept., 1914) frequently gives an initial dose of a pure staphylococcus aureus or albus vaccine, prepared and kept on hand in the laboratory. If the offending organism corresponds to the organism of the vaccine used in the first treatment, and if there has been an improvement, the stock vaccine is continued; in other circumstances the autogenous preparation is substituted.

Nagle (Monthly Cyclo. and Med. Bull., vol. iv, pp. 345-347, 1911) has been interested specially in the treatment of **chronic suppurative ears** by vaccine therapy. The results have been uniformly good. Out of 40 cases there was only 1 in which the vaccine failed to cure the discharge. The cause in this case was a staphylococcus. The author had not had much experience in the treatment of **adenitis** by this method, but up to the time of the paper the results were favorable. There had been less success in the treatment of nasal disorders, but improvement in some of them was marked, especially those cases of **atrophic rhinitis** with crusts and odor. After treatment there was only a slight amount of mucus, but no crusts, and the odor disappeared. To keep these patients in the improved condition it appeared necessary to continue the treatment.

Gilman Thompson (Assoc. Amer. Phys., May 11, 1909) has given an interesting account of a case in which the

use of staphylococcus vaccine was followed by remarkable results. The pathological condition was an infection of the forearm following a burn on the hand. **Septic pneumonia** developed, accompanied by suppuration of the wrist. In rapid succession appeared arthritis of the right knee-joint, pyonephrosis, and, finally, a spreading abscess which extended over the upper side of the chest wall and shoulder. The patient was in so critical a condition that the surgeons refused to operate, but treatment with bacterial vaccine was started. This was immediately followed by such improvement that operation was possible and 12 ounces of pus were removed from the abscess on the shoulder. Four subcutaneous inoculations were given at weekly intervals, three of 100 million each and one of 200 million. Immediate drop in the temperature followed the first inoculation, and subsequent rises were controlled by further injections. At the end of a month the patient's condition was normal and recovery complete.

Immunization by subcutaneous injection of autogenous colon bacillus vaccine, 50,000 bacteria up to a million or more, is recommended by C. R. Satterlee (N. Y. Med. Jour., June 17, 1916). The injections are given at 5 to 7 days' intervals. The patients quickly respond to this treatment.

Sherwood (N. Y. State Jour. of Med., vol. xi, No. 4, pp. 172-174, April, 1911) treated successfully a patient suffering with true **staphylococcus pyemia** following difficult labor in which forcible dilatation of the cervix was necessary. The staphylococcus was isolated in pure culture. In spite of 8 injections of a mixed vaccine con-

taining streptococci, staphylococci, and colon bacilli, there was no apparent benefit. An autogenous vaccine was made and its use was followed by immediate change in the condition of the patient. The dose was 40 million dead bacteria, and immediately after the second injection given the next day, consisting of 60 million bacteria, there was immediate reduction in temperature to the normal point. Three subsequent injections, 1 of 60 million and 2 of 40 million, were made at intervals of several days. There was a steady improvement in the anemia and the patient progressed rapidly toward a complete restoration of health.

Although Villandre and Rochaix (Annales de Med., Paris, Jan-Feb., 1918) found operative measures effectual in the treatment of 47 of the 61 cases of infectious complications following a war wound of the skull, among 450 skull wound cases, in 14 other cases, an inaccessible abscess developed in the brain. A cure was realized in 3 cases given autogenous vaccine treatment, although the abscess returned later in one of the cases. Nearly 50 per cent. died of the 11 not given the vaccine therapy. *The Staphylococcus aureus* was cultivated almost constantly from the projectiles and scraps extracted from the skull wound, even in those that healed apparently aseptically.

Sycosis.—Sycosis is one of the difficult diseases to treat with bacterial vaccines. It is a very chronic condition and results in diminished powers of resistance in the skin while irritation is kept up by local conditions such as nasal discharge and dust. At the same time the bacteria are so located with relation to the lymph-supply that it is difficult for the better quality of lymph

to reach them. For these reasons relapses are liable to occur. Results will be enhanced by methods assisting in overcoming such conditions, depilation by the X-rays or other means considerably aiding in the cure. But even this treatment may have to be prolonged.

Periostitis and Osteomyelitis. — When tuberculous bone disease is complicated by staphylococci, as in **psoas abscess**, vaccine treatment is of considerable assistance to the surgeon. The vaccine to be used should contain all varieties of bacteria present in the pus, and should be used in conjunction with tuberculin.

Prevention in Surgical Work. — Vaccines have been found of benefit before operation, especially in regions likely to become infected or where it is a question of operating upon an infected site which may be partly or entirely walled off. Such conditions are mastoid operations, operations upon the nose, the tonsils, appendiceal abscesses, pus tubes, sinuses, and fistulas of various kinds, empyema, etc. The vaccine to be injected depends, of course, upon the type of infection. The doses used also depend upon the general condition of the patient and the location of the focus of infection. A few attempts have been made to prevent postoperative pneumonia by vaccines. About 500 million staphylococci and from 150 million to 250 million streptococci are injected about a week before the operation. There are not enough records at hand to say what the ultimate conclusions may be in regard to this, but apparently good results have been obtained.

COLON BACILLUS INFECTIONS.

As the pneumococcus is almost constantly present in mixed infections

above the diaphragm, so the colon bacillus and its near allies are especially associated with diseases below the diaphragm, either alone or in conjunction with other bacteria such as the staphylococcus, streptococcus, pneumococcus, *Micrococcus tetragenus*, and *Bacillus pyocyaneus*. In treating infections due to the colon bacillus, it must be remembered that there are many varieties of this organism and, according to the findings of Avery, vaccine of one type has no effect on a condition due to infection by another type.

Avery isolated a culture of *B. aerogenes* from a case of cellulitis associated with *B. pyocyaneus* and *Streptococcus pyogenes*. A vaccine was made which was specific for this particular variety of infection, whereas the vaccine he made from *B. coli communis*, judging from the results attained, had no prophylactic or curative effect.

Allen (*loc. cit.*) has called attention to important facts in regard to the treatment of colon infections. These are:—

1. The fact, already mentioned, that the term *Bacillus coli* is a generic one. Thus Glenn (*Jour. Infect. Dis.*, p. 339, June 12, 1909) points out that other organisms, such as *Bacillus cloacæ*, which very closely resemble the *Bacillus coli*, may produce cystitis. The author himself has several times isolated bacilli from the urine in cases of bacilluria which were atypical. Thus, in one instance, the micro-organism resembled *Bacillus coli* in every detail except that it was rather positive than negative to Gram's stain, and failed to ferment certain carbohydrate media. The necessity of employing the autogenous vaccine whenever pos-

JACKSON'S CLASSIFICATION OF THE *B. COLI* GROUP.
(Jour. Infect. Dis., vol. viii, No. 2, pp. 241-9, Mar., 1911.)

		Dextrose.	Lactose.	Dulcete.	Saccharose.	Mannite.	Raffinose.	Motility.	Indol.	Nitrate reduction.	Liquefaction of gelatin in fourteen days.	Coagulation of milk.
B. <i>communior</i>	A ₁	+	+	+	+	+	+	+	-	-	-	+
B. "	A ₂	+	+	+	+	+	-	+	-	+	-	+
B. "	B	+	+	+	+	+	-	+	-	+	-	+
B. "	C	+	+	+	+	-	+	+	+	-	-	+
B. "	D*	+	+	+	+	-	-	-	+
B. <i>communis</i>	A	+	+	+	-	+	+	+	Slight.	+	-	+
B. "	B	+	+	+	-	-	+	+	+	+	-	+
B. "	C	+	+	+	-	-	+	+	+	+	-	+
B. "	D	+	+	+	-	-	-	...	+	+	-	+
B. <i>aerogenos</i>	A ₁	+	+	-	+	+	+	-	+	+	-	+
B. "	A ₂	+	+	-	+	+	+	+	-	-	-	+
B. "	A ₃	+	+	-	+	+	+	+	-	-	Positive after 26 days.	+
B. "	B ₁	+	+	-	+	+	-	-	-	+	-	+
B. "	B ₂	+	+	-	+	+	-	+	+	+	-	+
B. "	C*	+	+	-	+	-	+	-	+
B. "	D*	+	+	-	+	-	-	-	+
B. <i>acidi lactici</i>	A ₁	+	+	-	-	+	+	-	+	+	-	+
B. "	A ₂	+	+	-	-	+	+	+	+	+	-	+
B. "	B	+	+	-	-	+	-	+	+	+	-	+
B. "	C*	+	+	-	-	-	-	-	+
B. "	D	+	+	-	-	-	-	...	+	+	-	+

+ positive reaction.

- negative reaction.

* unknown varieties.

sible, and in default of this a highly polyvalent vaccine, is therefore obvious.

2. That not only is the vaccine, especially if heat be employed to secure sterility, highly toxic, but also that sinuses due to this organism show a marked tendency to close—a tendency which must carefully be counteracted, or rigors and other signs of autointoxication will ensue. Where this is likely to occur, an initial dose of 25 million should not be exceeded. Later, very much higher doses, even to 1 billion, may be safely employed.

3. It would appear that, after an autogenous vaccine has been employed for six to eight weeks, the living bacteria at the site of infection occasionally

manifest the power of elaborating a protective substance against the opsonin. This difficulty may be surmounted by taking fresh cultures and preparing a new vaccine.

4. The discharge of bacilli in cases of bacilluria may be markedly intermittent. It is never safe, therefore, to assume that infection has disappeared because one or two examinations of the urine point in this direction. Such examinations must be repeated at intervals of about three days for at least as many weeks. In this connection it must be remembered that certain cases which appear to be merely cystitis are in reality ones of renal disease, and may be complicated by tuberculosis; while

bacilluria may merely be evidence of colon infection elsewhere in the abdomen, as in the bowel, uterus, or old caseous abdominal glands.

If due regard be paid to these important points, it may be said that the prognosis is almost uniformly favorable in sinus cases, whether coming from the region of the liver and gall-bladder, appendix, pleura, or bone, provided that the appropriate surgical measures can be also pursued.

Among conditions most amenable to vaccine treatment may be mentioned **peritonitis, cystitis, urethritis, pyelitis and pyelonephritis, endometritis, enteritis, appendicitis, cholecystitis, subphrenic and hepatic abscess, empyema, and suppurative periostitis.**

The colon bacillus and streptococcus vaccines are recommended by W. W. Crawford (So. Med. Jour., June, 1912) in **acute appendicitis** in conjunction with operative treatment, 2 g. 50,000,000 dead colon bacilli on the first day, 100,000,000 on the second, 200,000,000 on the third, and 400,000,000 on the fourth. Many of his cases with tumor and fever either passed rapidly into the "cold" stage, where simple drainage, or drainage with appendectomy, became possible, or, when suppuration was slight, convalesced without drainage. In acute perforative appendicitis, if operated upon early, liberal doses of vaccine are helpful unless the patient is already overwhelmed with toxins. A. C. Guthrie (Brit. Med. Jour., Jan. 9, 1915) employed anticolon-bacillus serum and vaccine in 22 cases, which recovered without operative measures. Most of the cases were acute. The best dosage was 20 c.c. (5 drams) of anticolon-bacillus serum, 10 c.c. (2½ drams) being injected subcutaneously first in the right and then the left hypo-

chondriac region. A few days later 100 million colon-bacillus vaccine is injected in the deltoid region, to prevent recurrence. As other organisms may be causative, the "fixation of complement test" should be tried, using the patient's serum and the most probable organism (*B. coli*, pneumococcus, streptococcus). A corresponding serum or vaccine is then used. A striking relief of pain and a feeling of well-being followed the serum injections.

Emery (Imm. and Spec. Ther., pp. 394-395) says: "Vaccine treatment cures all symptoms and reduces the pus and bacilli present in the urine to a small fraction of its original amount, but fails to remove them entirely."

Emery thinks that, next to staphylococci, colon infections yield best to vaccine therapy.

Hugh Cabot (Trans. Amer. Assoc. of G.-U. Surgeons, vol. v, pp. 288-292, 1910) reports upon the use of vaccine in the treatment of infections of the urinary tract with the exception of tuberculous and gonococcus infections. The report comprises chiefly those infections due to the colon bacillus and pyogenic cocci. Cabot says that surprisingly different results may be obtained in estimating the therapeutic value of vaccines according to the point of view of the investigator. The general practitioner is particularly interested in the *relief of symptoms* and will be satisfied when this end is accomplished. The clinical bacteriologist will be interested in the ability of vaccine treatment to rid the urine of bacteria. The very varied conclusions of different observers have been largely due to this different bias. Several of the cases in the series reported by Cabot had already been reported as cured by other men,

though their urine still contains bacteria. Thirty cases were under observation; the colon bacillus was the infecting organism in 22; the colon bacillus mixed with the streptococcus or with the staphylococcus was found in 3. The streptococcus was present alone in 2, the *Staphylococcus albus* and streptococcus in 2, while the *Staphylococcus albus* was in pure culture in 1 case. Treatment was continued for from two months to two years, the average time being slightly less than ten months. In 19 cases there was definite relief of symptoms varying from marked improvement to complete *symptomatic cure*; in the remaining 11 cases there was no definite relief, though many of them showed transient improvement which may or may not have been due to the treatment. In all cases the culture has been obtained from two months to two years after the cessation of the treatment. Three are and have remained free from bacteria; the remaining 27 all showed bacteria and were therefore not benefited as to the presence of bacteria. The results were practically the same whether the lesion was in the upper or lower urinary tract.

Irons (Jour. Amer. Med. Assoc., vol. lv, No. 20, pp. 1717-1719, Nov. 12, 1910) says that something over 50 per cent. of **urinary infections** are due to the colon bacillus, and in still more this organism is associated with other bacteria. The use of vaccines in infections of the urinary tract, especially those due to the colon bacillus, has received much attention during the past year, and the reports indicate that good may be accomplished in the alleviation of local distressing pyuria

and general symptoms. In mixed infections mixed vaccines have been used with advantage. It frequently happens in the treatment of colon infections that the bacilluria persists after the subsidence of clinical symptoms. Colon infections of the **prostate** which have resisted all ordinary treatments have, in a number of instances, been improved by vaccine.

Hartwell and Streeter (Boston Med. and Sur. Jour., vol. clxii, No. 13) have treated 19 cases of infections of the urinary tract with bacterial vaccines. Nine of them were infections of the bladder alone, and 10 of the bladder and kidney including the ureters. The *Bacillus coli* was present in 12 cases, *Bacillus coli* and streptococcus in 4 cases, streptococcus alone in 1 case, streptococcus and *Staphylococcus albus* in 1 case, *Staphylococcus aureus* and *albus* in 1 case. Autogenous vaccines were used in all cases. The initial dose was 25 to 50 million, and this dose was progressively increased. Some patients received doses as large as 800 million to 1200 million *B. coli*, but the usual maximum was 200 to 400 million. In children the initial inoculation was 10 million and the maximum was proportionately lower. The writers conclude that vaccines are efficient in relieving the symptoms in mild forms of cystitis; they have a less marked effect on pyuria, and are without value in severe forms of cystitis. They probably hasten recovery from pyelitis.

Hale White and Eyre ("Proceedings of the Royal Society of Medicine," p. 146, June, 1909) have reported excellent results in a severe case of **cystitis** and double **pyelitis**

accompanied by vomiting, high fever, and rapid pulse. The use of an autogenous vaccine resulted in immediate improvement. A dose of 5 million was followed four days later by a dose of 30 million, and ten days later this was followed by one of 250 million.

In non-surgical infection of the kidneys and ureters, G. J. Thomas (Urol. and Cutan. Rev., xx, 127, 1916) advises a careful search for foci of infection such as tonsils, teeth, abscesses, furunculosis, bone infections, etc., before urologic treatment is instituted. In the local treatment, lavage of the renal pelvis and ureters every 4 or 5 days is most frequently used, with 0.5 to 3 per cent. silver nitrate. Autogenous vaccine and urinary antiseptics are also given. Of 150 cases, 46 per cent. were thus improved and 18 per cent. more cured.

Rawl (Med. Rec., p. 359, Feb. 24, 1912) has observed 18 cases of *B. coli* infection in the last two years and reports 8 in full. These show that the *Bacillus coli* may be the cause of acute urinary infection in health, in the puerperium, and in postoperative gynecological cases. He says that hematogenous infection is quite common. The infection may be primary or secondary.

Of his 18 cases 2 were in health, 2 post partum, and 14 postoperative.

The primary focus of the postoperative cases when not in the urinary tract was as follows:—

Infected ectopic gestation and abdominal wound	1 case.
Appendix and pelvic abscess	1 "
Gall-bladder and carcinoma of stomach	1 "
Appendix	1 "
Pelvic abscess and tubal disease	1 "
Perinephritic abscess	1 "

There was probably hematogenous rather than ascending infection in all

these cases with the possible exception of the last; treatment was chiefly with urotropin, sodium benzoate, and vaccines.

Hugh Roger-Smith (Jour. Vaccine Therapy, p. 95, March, 1912) has had several patients with colon bacilluria, all of whom received autogenous vaccine. One man of 40 had had 7 attacks of "influenza" in the preceding nine months. Urine was loaded with *B. coli*; urotropin and silver nitrate irrigations of bladder improved the condition, but colon bacilli persisted and he had slight fever at times. Prepared vaccine was given, 50 to 250 million. After 12 injections of vaccine in doses of 50 to 250 million the urine became sterile and all symptoms disappeared. Symptoms of pain and frequency of micturition disappeared in another case with the urine full of *B. coli* after 12 injections of vaccine, a previous course of urinary antiseptics having failed. In a man of 74 who had had a prostatectomy several years previously, intense bladder irritability and purulent discharge from which *B. coli* was cultivated cleared up under autogenous vaccine. In a similar case the urine is still full of bacilli, but vaccines have improved the symptoms and are to be continued.

M. J. Synott (Med. Rec., p. 759, Oct. 14, 1911) reports *Bacillus coli* infections in the urinary tract, producing nephritis, pyelitis, cystitis, and infections in other parts, such as postoperative abscesses following appendectomy, and are all suitable cases for inoculation treatment. Autogenous vaccines are necessary, in Synott's opinion, as stock vaccines have been unsatisfactory. Correct applications of *Bacillus coli* vaccine by skillful hands in acute bacillus coli

pyelitis, cystitis, ureteritis, and nephritis, with fever and other evidences of systemic infection have produced results ranging from a complete cure to considerable amelioration of the symptoms related to micturition, the local discomfort, pyrexia, anemia, and loss of weight. The dose of the *Bacillus coli* vaccine is 5 to 20 million every five to seven days.

David J. Davis (Jour. Infect. Dis., vol. vi, No. 2, pp. 224-244, April 1, 1909) believes that his results appear distinctly to favor the inoculation treatment of ordinary infections caused by the colon bacillus. Several cases treated by him have responded favorably to such treatment. In 1 patient, pus and bacilli had been present in the urine for over five years. After nearly four months' treatment with weekly doses of vaccine, bacilli entirely disappeared and the patient is now perfectly well.

Butler Harris called attention in 1908 to the treatment of **mucous colitis** in which he had obtained good results. This was confirmed by Hale White and Eyre in 3 cases. The pain is lessened, the diarrhea, mucus, and blood diminished, and the general health much improved. It would appear that in bacterial vaccines an important adjuvant is afforded to the treatment of this very persistent trouble.

A. H. Drew (Jour. State Med., London, July, 1918) treated with great success 15 cases of **membranous colitis** by means of autogenous vaccines. The patients all exhibited most of the classical symptoms of this disease. All the patients with the exception of one, passed casts which examination showed to consist of a mucoid material, containing many goblet cells, leucocytes, and, in some cases, acicular crystals.

The membrane in all cases swarmed with bacteria, of which the Gram-positive forms predominated. In fourteen of the cases the enterococcus was observed together with *streptococcus fecalis*. In no case could any evidence of agglutination be obtained with either organism, but in all cases a low opsonic index was obtained with the enterococcus. Complement fixation was obtained with 4 out of the 6 cases tested, using the enterococcus as an antigen. The writer found that many patients are extremely susceptible to the enterococcus, hence initial doses of vaccine of not more than 2 to 3 million cocci should be given. The treatment should be continued with gradually increasing doses till 500 million cocci can be injected without producing reaction.

Bonny (Clin. Jour., Aug. 19, 1908) emphasizes the great frequency and the gravity of the presence of *Bacillus coli* either alone or with other organisms in **puerperal sepsis**. He says that care should be taken to discriminate between a case of *true* puerperal sepsis and one of a *localized infection* of the uterus by the colon bacillus. Delay in the latter case while the results of treatment upon general lines are being awaited is excusable; in the former case, unpardonable. Should blood-cultures confirm the bacteriological findings in the uterine discharge one should not hesitate to have immediate recourse to vaccine therapy. The worse the condition of the patient, the greater the necessity for prompt action. Everything depends upon the reserve strength of the patient. If this is adequate to tide the patient over for two or three days, an autogenous vaccine should be used in doses from 5 to 10 million. In twelve to eighteen hours the temperature should drop from 2°

to 3° F.; the pulse and general condition should improve. Any sharp rise or a steady rise continued over twelve hours should be a signal for a fresh injection.

Wright and Reid (Lancet, vol. i, p. 159, 1906) treated 2 cases of **cholecystitis**, both of which were cured. The first case was one of obstructive jaundice which had not been relieved by operation. The colon bacillus was isolated from the bile and an autogenous vaccine made. Three injections sufficed to obtain a cure. The second case was one in which fourteen stones had been removed two months previously. The wound would not heal and the patient's condition was generally poor. Vaccine treatment produced a slow but complete recovery.

Turton and Parkin (Lancet, vol. ii, p. 1130, 1906) treated a patient whose condition was diagnosed as pancreatic disease and who was operated upon. His pancreas was found normal. The gall-bladder was distended and contained a large stone. From the secretions *Bacillus coli* was isolated. Because of his slow progress an autogenous vaccine was prepared and, after three injections of 500 million each, rapid and complete recovery resulted.

The value of **preoperative vaccination** in order to increase the resistance of the patient to possible infection (especially when an infected focus is liable to be found) has already been mentioned. It is always advisable in such cases to use a mixed vaccine, and this vaccine should contain the colon bacillus.

MENINGOCOCCUS.

The recent epidemic of meningitis in Texas and neighboring States has stimulated great interest not only in

the use of antimeningococcus serum for curative purposes, but also for prophylaxis. A vaccine standardized by Wright's method and prepared by the suspension of killed meningococci in normal saline solution has also been used for prophylaxis. Statistics are not at present available, but it seems likely that this vaccine will compare favorably with others intended for the same purpose. Such a vaccine has already been used therapeutically in a few cases. Emery ("Immunity and Specific Therapy," p. 374) reports its use in 4 cases with 3 recoveries and 1 death. He believes the vaccine is well worthy of a trial. The most striking thing about the injections was the clinical improvement which followed almost every dose. This occurred too frequently to be a mere coincidence, and, as all the patients were young children, the question of mental influence need not be considered. The initial dose was 250 million; the following doses were increased to 500 and 1000 million, respectively. No bad effects were noticed. Murata says: "It need hardly be pointed out that no form of specific treatment will cure the obliteration of the foramen in the roof of the fourth ventricle and consequent hydrocephalus which is so frequently present in these chronic cases."

In a severe case of pneumococcal meningitis, A. C. Brown (Lancet, Sept. 16, 1916) had excellent results from the use of a stock pneumococcus vaccine. Lumbar puncture showed a thick, opaque fluid with pneumococci. In all, 5 doses were given, and complete recovery followed.

Hector Mackenzie, Rundle, Mottram, R. S. Williams, Orr, and A. E. Wil-

liams had previously reported cases of cerebrospinal meningitis successfully treated. In that of the last named observer, the patient was admitted on February 27th. The first inoculation was made on March 11th. From the time of admission to the commencement of the vaccine treatment the condition had become progressively worse. The general nutrition failed rapidly, until no subcutaneous fat could be detected on pinching the skin. With the exception of a marked remission of the temperature of the body no marked change was observed in the clinical manifestations during the succeeding forty-eight hours. On the 14th, however, a definite decrease in the degree of extension of the head and neck was noted. The spine could be straightened with the exercise of moderate force, and lateral movements of the head were made voluntarily. The first dose contained 200 million meningococci; the second dose, given on the 16th, was 500 million; the third dose, given on the 21st, 510 million. Two more doses were given at eight-day intervals, each being 530 million. The writers believe that so rapid and complete a recovery with no definite relapses or involvement of the special senses could scarcely have been expected with the customary methods of treatment.

Meningococcus vaccines will undoubtedly be given a more extensive therapeutic trial, while their use for prophylaxis may prevent the occurrence of another widespread epidemic.

BACILLUS PYOCYANEUS.

The *Bacillus pyocyaneus* is responsible for primary and secondary infections in various parts of the body.

Waite (Jour of Inf. Dis., vol. v, No.

5, pp. 542-565, Dec., 1908) has carefully reviewed the literature. He finds that this organism has been reported as the cause of infections in practically every part of the body, the eye and ear, respiratory and digestive tracts, serous membranes, meninges, genito-urinary tract, skin, liver, bones, and joints, and a number of more general infections have been reported, such as abscesses in various parts of the body. The lesions may be general or localized, mild or severe.

Grace-Calvert (Proc. of the Royal Soc. of Med., vol. iii, discussion on Vaccine Therapy, p. 160, 1910) has used a vaccine for the treatment of **middle-ear disease** where the sole organism was the *Bacillus pyocyaneus*. He met with success up to a certain point, but treatment had to be temporarily withheld on account of an attack of hay fever. After the vaccine was stopped by the advice of the surgeon the ear began to discharge more freely and the cause of the trouble was still limited to the *Bacillus pyocyaneus*.

In 1908 Trimble (Jour. Kans. Med. Soc., viii, p. 371, 1908) reported 5 cases of **suppurative otitis media**; 2 were due to the staphylococcus; 1 to *Bacillus pyocyaneus*, 1 was a mixed staphylococcus and pyocyaneus infection, and 1 contained streptococci. Good results were obtained from the use of vaccines, in all except the case showing the *Bacillus pyocyaneus* in pure culture.

Kolmer reports that the *Bacillus pyocyaneus* was found in 20 per cent. of cases of suppurative otitis media discharging for four weeks or longer. This organism is believed by many to be a practically harmless saprophyte, feeding on tissues killed by some other

organism. In 10 per cent. of the cases this bacillus was found from the third to fourteenth day of discharge, alone or in combination with some other organism. The results of vaccine treatment were satisfactory in these early cases and while the administration of a vaccine prepared from this organism may have been merely coincident to a rapid cure, yet he cannot agree with those who claim the vaccine to be practically without effect. On the other hand, of the 15 patients dismissed from the hospital with persistent discharging ears, in 13 the *B. pyocyaneus* was found in pure culture and the vaccine did not produce favorable results.

MacWatters (Proc. of the Royal Soc. of Med., vol. iii, p. 178, 1910) believes that many cases of so-called **rheumatism** may be simply an expression of a toxemia due to bacterial invasion of some remote tissue by one or a variety of organisms. He recalled a case of what was considered to be **muscular rheumatism** which yielded *Bacillus pyocyaneus* from the urine.

Groves (Brit. Med. Jour., vol. i, pp. 1169-1170, May 15, 1909) reports a case of *Bacillus pyocyaneus* **pyemia** successfully treated by vaccine. A boy of 8 years had nine months before developed two abscesses, one over the right Poupert ligament and the other on the inner side of the left thigh. The right abscess healed quickly, the left more slowly, and when it had disappeared the left hip-joint remained painful and stiff. Upon examination there was marked adduction of the thigh and about one inch of real shortening. The left hip was the seat of firm fibrous ankylosis. The acetabulum was enlarged upward possibly by the process

of caries affecting its superior margin. At operation the left hip-joint was exposed, the diseased bone was scraped away, and the adducted position was forcibly corrected. The day after the operation the temperature rose to 103° and remained near this point for five days, after which it underwent characteristic hectic fluctuations. Four days after the operation swelling of the right thumb developed, which when opened was found to contain thick, gelatinous pus. During the next two months other abscesses developed, chiefly in the region of the pelvis. Finally a bacteriological examination was made and a pure culture of the *Bacillus pyocyaneus* was obtained. An autogenous vaccine was prepared and an initial dose of 40 million bacilli was injected, with no appreciable result. Eight days later 60 million bacilli were injected; the next day the temperature descended to normal and has remained so ever since. The injections were continued at from ten- to fourteen-day intervals until four more doses had been given. From the date of the second injection the boy's whole condition greatly improved: he slept quietly, took his food well, became plump and well nourished, and all the abscesses and sinuses healed except a small one on the inner side of the left thigh, which at the time the case was reported was superficial.

MICROCOCCUS NEOFORMANS.

The statement of Doyen that he had found in the *Micrococcus neoformans* the true cause of **cancer** has not been accepted. That it is one of the frequent secondary infecting organisms there can scarcely be any doubt. Jacobs and Geets (Lancet, vol. i, p. 964, April 7, 1906) were able to isolate the *Micrococcus neoformans* from 90

per cent. of the tumors they examined, and have succeeded in producing localized or generalized lesions in 30 per cent. of the mice and white rats inoculated with young and vigorous cultures of the micro-organisms. Although the *Micrococcus neoformans* cannot be considered as the primary infecting agent in carcinomatosis, yet there is reason to believe that much of the pain and swelling and the inflammation of the tumor and much of the so-called cancerous cachexia are due to it. We cannot hope to strike at the root of the evil by vaccine treatment, but cancer, particularly inoperable cancer, may sometimes be relieved and the patient benefited or his case brought within the zone of operation by the carefully guarded use of properly prepared and standardized neoformans vaccine. Doses of 25 to 50 million are recommended, and the decline of the positive phase is the indication for another injection.

Wright treated a patient suffering from cancer of the larynx with apparent improvement but ending in death. Jacobs and Geets (*loc. cit.*) treated 37 cases. They found the opsonic index to be generally below the normal and to rise after injections of the vaccine. The treatment seemed to decrease the surrounding infiltration and reduce the size of the nodules. There was great improvement in the appearance and general condition of many of the patients and a diminution of pain was noted. Their results are tabulated as follows:—

"Cure" maintained after several months	
in	7 cases.
Lasting improvement in	12 "
Transient result in	7 "
No result in	11 "
Total	37 "

These authors do not advise the use of the vaccine when the opsonic index of the patient shows no rise after one or two injections. They then consider the defensive powers so exhausted that stimulation by any method is impossible. Continued injections under such conditions may lead to a dangerous cumulation of the negative phase, and to early death.

The opinion at the London Cancer Hospital is that as a curative agent a vaccine of the *Micrococcus neoformans* is valueless, and its employment has therefore been entirely abandoned at that institution.

TUBERCULIN.

Since the period during which it was almost universally condemned tuberculin has gradually come into favor, until at present it is used extensively for the diagnosis and treatment of tuberculosis. The exact mechanism of the curative effect of tuberculin is still subject to debate. It is believed, on the one hand, that the products manufactured by the stimulated cells are bactericidins and opsonins, and that these act directly upon the tubercle bacilli. Another theory holds that the tuberculin stimulates the production of substances which neutralize the metabolic products of the tubercle bacilli, enabling the body cells to resist their effects and remain unharmed by them, even though the bacilli are still present and growing in the body. It is possible that tuberculins representing the metabolic products of tubercle bacilli when grown upon culture media may have the latter effect as a predominant feature, while the new tuberculins of Koch containing the bacilli themselves may act more as we believe bacterial vaccines act, *i.e.*, as opsonogens. There

is much to be said in favor of Law-
rason Brown's idea that a mixed tuber-
culin should be preferred.

In the treatment of **surgical tuber-
culosis** the results with tuberculin
have been very satisfactory. In
pulmonary tuberculosis it is believed
that proper rest, fresh air, and good
food supplemented by tuberculin yield
better results generally than the same
measures without tuberculin. Much
skill is required in selecting the
proper patients to receive tuberculin
and in determining the size of the
dose to be administered, the intervals
between doses, and the amount of
rest or exercise to be taken by the
patient.

The study of **mixed infections**
is receiving more and more attention,
and mixed vaccines of appropriate com-
position are reported to be followed by
remarkable success. Caulfeild, Petit,
and others have demonstrated con-
clusively that great benefit may follow
the use of bacterial vaccines even
without tuberculin. That tuberculin is
capable of doing a great deal of harm
if carelessly used—that it is a two-
edged sword—has been repeated so
often that to those who do not have an
opportunity of seeing the effects of
its careless administration the saying
seems trite. Nevertheless, it cannot be
denied that many persons have been so
impressed by the harm tuberculin may
do, that their anxiety to do no harm
has resulted in their doing little good.
The work suggested by White and Van
Norman, if it is confirmed, should be
utilized more widely. They believe
much valuable time is lost in giving
doses of tuberculin much smaller than
the proper therapeutic amount should
be. In default of the practical applica-

tion of opsonic index methods the **only**
other indication the physician has con-
cerning the amount of autoinoculation
that is going on is the temperature
record, and the individual susceptibility
to tuberculin as determined only by
trial and error. The doses of tuber-
culin used at the present time follow
pretty closely those worked out by
Wright. Bacillen emulsion is generally
administered in initial doses of about
 $\frac{1}{50000}$ to $\frac{1}{10000}$ mg., while old tuber-
culin is given in quantities somewhat
larger. The doses are generally given
at intervals of seven to ten days,
and the slightest febrile or systemic re-
action following a dose is taken as an
indication that it was too large. The
injection is usually given subcutane-
ously exactly as are bacterial vaccines.
Efforts have been made to give it by
mouth, and administration by inunction
has been attempted.

Kinds of Tuberculin.—Many at-
tempts have been made to elaborate a
product containing the proper antigenic
substances for the specific treatment of
tuberculosis, with the result that in-
numerable forms of tuberculin have
been presented to the medical profes-
sion. The tuberculins may be divided
into three great classes: those that con-
tain the products of metabolism of the
tubercle bacillus, those that contain
substances of the tubercle bacilli them-
selves, and those consisting of both
metabolic products and tubercle bacil-
lary substances. The tuberculins con-
sisting of the metabolic products of the
tubercle bacillus are O. T. and B. F.
The old or original **tuberculin** (O. T.)
of Koch is prepared from cultures of
the tubercle bacillus 6 or 8 weeks old,
grown upon 5 per cent. glycerin bouil-
lon. After sterilization the culture is

evaporated to one-tenth its bulk. It is then filtered to remove the bacterial bodies. The resultant filtrate is old tuberculin. The bouillon filtrate (B. F.) differs from old tuberculin only in that no heat is used for its preparation. It is merely a sterile filtrate from well-grown bouillon cultures.

To distinguish them from the older preparation elaborated by him, Koch called the tuberculins containing bacillary substances, which he described in 1897, **new tuberculins**. There are two of these—the first, T. R., contains the washed residue of ground tubercle bacilli suspended in 20 per cent. glycerin. The final product is so diluted that the amount of solid substance is 2 mg. per c.c. Bacillen emulsion (B. E.) is more like the ordinary bacterial vaccines in use at present. The bacteria are treated merely by grinding in a hard-porcelain ball mill for a long time, the powder being then suspended in 50 per cent. glycerin. It is diluted so that each c.c. of the tuberculin contains 5 mg. of powder. In stating the dosage of a tuberculin it is advisable to speak of it in quantities of the finished product only, without reference to the amount of solid bacillary substance contained in a cubic centimeter; for instance, $\frac{1}{10000}$ mg. of bacillen emulsion means this amount of the completed tuberculin.

As stated above, Brown and others have suggested the use of a mixed tuberculin. That preferred by Brown is composed of B. E. and B. F.

A few phthisiologists prefer to use a so-called "heterologous" tuberculin; that is, in treating infections caused by the bovine type of bacillus they

use a tuberculin prepared from human tubercle bacilli, and *vice versa*.

The Diagnostic Reactions.—The only tuberculin used to any extent for diagnostic reactions is O. T. When tuberculin is injected even in large doses into a person free from tuberculosis no symptoms are produced. If, however, tuberculosis is present there follows, within the course of a few hours, a rise in temperature and a feeling of general malaise. The general disturbance is accompanied by a local reaction at the point of injection, which becomes red and exhibits a swollen appearance. Tuberculous individuals react to very minute quantities of tuberculin and, when properly used, this phenomenon is of great diagnostic value. The following method is that followed by Roth-Schulz (from "Pulmonary Tuberculosis," Francine, 2d ed.):—

"The temperature and pulse rate of the patient to be investigated are carefully noted for from four to seven days, after which, in the event of these being normal or only very slightly elevated, an initial hypodermic injection is given of 0.5 mg. old tuberculin. If no reaction follows this in from three to four days, the same dose is usually repeated, particularly if any symptoms indicative of a mild reaction have occurred. If the temperature shows any irregularities, a longer period is allowed to elapse and the same repeated a third time. Usually, however, in the absence of reaction, the second dose is increased to 1.25 mg. This amount may be repeated after the lapse of two or three days without reaction, or the dose increased to 2.5 mg. This maximum dose may again be repeated. The

importance of repeating the same dose is emphasized, as often a merely suggestive reaction after the first administration may be followed by severe symptoms after the second dose.

"A rise in temperature of 1° F. (0.5° C.) above the previous maximum is considered positive, but great importance is attached to the development of general and local phenomena. Even in the event of only a slight rise in temperature, the development of râles where they were previously absent, or the occurrence of general symptoms, is considered positive.

"There is no danger in the test as outlined, even when incipient or latent tuberculosis is present, as the fever reaction is usually moderate and soon disappears if the patient is kept in bed a day or so. The advantage of making a diagnosis in doubtful cases before physical signs or symptoms are available cannot be overestimated in relation to the prognosis of treatment."

Local reactions to tuberculin depend upon the fact that the cells of a tuberculous individual are highly sensitized, so that when tuberculin is brought into contact with them it is immediately split up. The poisonous part, being set free, exerts a local irritating action upon the tissues. This is characterized by hyperemia and inflammatory changes at the point of application.

The Cutaneous Reaction.—Von Pirquet pointed out the fact that, upon scarifying the skin of a tuberculous subject and applying a solution of tuberculin, there appears an area varying from a local hyperemia to an intense inflammatory reaction. Many times the reaction is characterized by

the appearance of a small papule, the disappearance of which is followed by a brownish pigmentation. The reaction is not attended with fever, malaise, or any other general symptoms.

The cutaneous method consists in putting a drop of pure or diluted old tuberculin upon the skin and then making a slight abrasion of the skin under the drop of tuberculin with a lancet, quill, or von Pirquet's "scratcher" (Schäber). Only the most superficial layers of the epithelium need be removed, just sufficient to open the superficial lymph-channels. It is undesirable to draw blood. The technique to be employed is practically the same as that used in vaccination against small-pox, and the dangers of secondary infection are exceedingly slight. At a distance of about one inch a control abrasion should be made under a drop of 50 per cent. glycerin and 0.1 per cent. phenol in physiological saline solution. Care should be exercised not to carry tuberculin on the instrument to the control. Where large numbers of patients are vaccinated a platinum-iridium instrument that can be heated is recommended.

The value of the von Pirquet reaction is variously estimated. It is extremely delicate, and on that account often reacts with individuals who appear to be practically free from tuberculosis. However, as pointed out by Hamburger soon after the introduction of the test, "it is quite difficult to find an adult free from tuberculosis, which explains the great frequency of von Pirquet's reaction in adults." Its greatest value is in the diagnosis of tuberculosis in children.

F. Feer in a study of "the value of cutaneous and conjunctival reactions in children," based on many observations, states that "a positive von Pirquet reaction is without doubt specific for tuberculosis. Especially valuable is the test during the first three years; after this time a negative result is of more value than a positive one. Care must be taken to distinguish the spurious from the true reactions. Reactions which disappear in twenty-four hours are not specific."

Characteristic Cutaneous Reaction.—Jules Lemaire has identified or distinguished three grades of the von Pirquet reaction which he describes as follows:—

"Feeble reaction: Hyperemic zone—4 to 6 mm. in diameter, in the center of which is a papule; the skin slightly swollen and hard.

"Medium reaction: Hyperemic zone—6 to 12 mm. in diameter; numerous papules very prominent. The skin is quite edematous throughout the area. The redness persists for several hours.

"Strong reaction: All of the foregoing conditions are very much exaggerated. The area of reaction gives a very resistant sensation to touch and the zone of hyperemia extends from 2 to 3 cm. If the subjacent edematous area is pronounced, it gives an appearance of urticaria. Occasionally at the points of scarification there is an exudate of a serous fluid."

A positive response was obtained by De la Torre (Prensa Med. Argentina, Nov. 10, 1918) in 71 out of 171 children tested in an orphan asylum. About 20 per cent. of the infants under 1 year gave a positive response, including one only 2 months old; 34.4 per cent. of those between 1 and 2; 42 per cent. of those between 2 and 5;

47.6 between 5 and 10, and 57 per cent. between 10 and 15. Of the total positive responses only 52 were obtained at the first test; 11 at the second, and the others at the third to the sixth application of the test. The first 3 tests were made by the skin technique, the others by Mantoux's intradermal method.

For the purpose of checking up the von Pirquet test with some other of the cutaneous *tuberculin tests*, Mantoux's intracutaneous injection was done by Reiss (Arch. of Pediat., Dec., 1918) on children. A solution of old tuberculin in normal salt solution, 2 minims or 0.005 mg., was used for the Mantoux; normal salt solution for the control. Nineteen of the 120 cases gave positive reactions; one doubtful reaction was classed as negative. The von Pirquet test was never positive in the absence of a positive Mantoux. It was negative in three cases which gave a positive Mantoux. Seventeen of the nineteen positives displayed adenopathy, and of these thirteen, only in two were the posterior cervicals enlarged. The writer concludes that the intracutaneous tuberculin test when carefully performed seemed somewhat more reliable than the von Pirquet. Tuberculous meningitis cases apparently do not respond to cutaneous tuberculin tests (four cases after repeated tests uniformly gave negative results). The presence of posterior cervical adenopathy in children is highly suggestive of tuberculous infection.

The von Pirquet and Moro tuberculosis tests are regarded by J. W. Allan (Glasgow Med. Jour., Jan., 1919) as helpful aids to diagnosis; nothing more. They have the ad-

vantage also that they may be used without fear of doing harm.

The Moro Reaction.—The following diagnostic reaction as described by Moro has attracted considerable attention among clinicians:—

“A tuberculin ointment is prepared by a combination of equal parts of old tuberculin and anhydrous lanolin. The lanolin base is selected because with this material it is possible to prepare a very concentrated ointment. The mixture is made at a temperature of from 20° to 30° C.

“Ten grams of ointment is sufficient for 100 tests. The point of application is over the skin of the abdomen or over the breast, near the mammæ. The ointment is energetically rubbed on to the skin for one-half to one minute. The area of the part treated is about two inches. The positive effect is noted by the eruption of a granular or a papular efflorescence at the point of application.”

Moro divided the reaction into three groups:—

“First.—A weak reaction. At the point of application there appear, after twenty-four to forty-eight hours, seldom later, single, distinctly red nodules, from two to ten in number, of a diameter of 1 to 2 mm. This efflorescence disappears after a few days, and at no time has caused any itching or other irritation.

“Second.—The medium reaction. At the point of application there appear, in the first twenty-four hours, numerous (100 or more) miliary or larger red nodules, about 3 mm. in diameter. The skin surrounding the eruption is intensely red. The reaction is confined to the point of application, and is accompanied by considerable itching. This disappears after a few days.

“Third.—The strong reaction. At the point of application there appear, within a few hours, 100 or more large nodules or papules, upon an inflammatory base. The dermatitis associated with it is accompanied by intense itching. Many of the eruptions form an exudate and often reach a size of from $\frac{1}{8}$ to $\frac{1}{4}$ inch in diameter.

“The reaction is not only confined to the point of application, but extends into the surrounding areas. After a few days the papular efflorescence dries up, leaving a brownish pigmentation of the skin which remains for several weeks. General symptoms, namely, rise of temperature, etc., do not accompany the reaction.

“The strong reaction occurs seldom. In 37 positive reactions, we only observed it 3 times, 2 of these cases being scrofulous and 1 caries of the bone. The weak reaction we observed 25 times and the medium reaction 9 times in the 37 cases.

“The most distinct reaction is observed in scrofulous conditions and tuberculosis of the bones. Weaker reactions occur most often in cases of tuberculosis of the lungs.

“An important factor in determining the stage of the reaction is, without doubt, the sensitiveness of the skin.”

Moro gives a table showing the value of the percutaneous reaction compared with the cutaneous vaccination of von Pirquet. In 16 cases of undoubted tuberculosis, 12 were positive with the percutaneous reaction and 14 positive with von Pirquet's reaction. In 12 cases of scrofulous conditions, 6 reacted “positive” to the percutaneous reaction and 6 “positive” to the von Pirquet reaction. In 20 cases of probable tuberculosis, 12 reacted “positive” with the percutaneous and 12 reacted

"positive" with the von Pirquet reaction. Of 25 cases of non-tuberculous patients, 3 reacted "positive" with the percutaneous and 8 reacted "positive" with the von Pirquet. Of 68 cases, 21 of children of suspected tuberculosis reacted and 4 children with manifest tuberculosis.

"The ointment reaction is strongly specific. All cases that gave a tuberculin-ointment reaction also gave the cutaneous described by von Pirquet. A positive ointment reaction without a positive von Pirquet reaction I have at no time observed. The ointment reaction is absolutely harmless. The occurrence of itching at the point of application occurs only relatively seldom."

The Calmette or Wolff-Eisner conjunctival reaction cannot be recommended owing to the danger incurred.

Therapeutic Uses of Tuberculin.—

The indications for the therapeutic use of tuberculin are all forms of chronic tuberculosis in their earlier stages, no matter where they are localized. **Pulmonary, glandular, ocular, urogenital tuberculosis, lupus, and tuberculosis of the bones and joints,** are all suitable for tuberculin therapy *in properly selected cases*. Of course, other appropriate therapeutic and hygienic measures must essentially be combined with the tuberculin treatment.

Tuberculin was found by Verheyden (Brit. Jour. Ophthal., Apr., 1918) to give good results in **phlyctenular kerato-conjunctivitis**, especially as regards photophobia, blepharospasm, lacrimation, but does not prevent relapses, although the latter when they occur are milder; the usual local treatment is also employed. **Scleritis and episcleritis** are more rebellious; the other etiologic factors of these

affections should be eliminated before having recourse to tuberculin. One case of **iridocyclitis**, probably bacillary, recovered by local treatment and 6 injections of tuberculin. One case of **paralysis** of the third pair, of tubercular origin, with double ptosis, paralysis of the right superior rectus and slight diplopia, recovered after a relapse during the course of the treatment, which consisted of 6 injections of tuberculin (0.001 to 0.009) made during an interval of 9 months.

The tuberculin treatment in 20 cases of different forms of **ocular tuberculosis** observed by Wimmer (Semana Medica, Aug. 29, 1918) illustrated the excellent results that can almost be counted on with tuberculin treatment as an adjuvant to the usual measures. The mode of reaction in each patient should be carefully studied and the tuberculin gaged accordingly. The greater the reaction, the more cautious should be the dosage of the tuberculin. The most promising cases are those in which there is an intense reaction but without modification of the pulse, in which the congestion and the fever yield to small doses, and the weight shows a very slow but progressive increase.

The use of tuberculin is contraindicated in acute miliary tuberculosis, in tuberculous meningitis, in severe cardiac complications, and *perhaps* in epilepsy.

Tuberculin therapy as practised by Trudeau has gained favor among American physicians, but on prudent lines and beginning with very minute doses, even where its use is clearly indicated. As stated by:—

S. G. Bonney (Jour. Amer. Med.

Assoc., Oct. 21, 1916) urges that vaccine therapy should by no means be permitted as a routine measure in the treatment of tuberculosis. It has a place as a tentative procedure in a class of cases subject to certain modifying limitations. The careful adjustment of the dosage is vitally important. The results obtained are very uncertain. The gain established in a few cases is, however, impressive. The proportion of cases exhibiting improvement is disappointing. Vaccines not infrequently are shown to possess vast possibilities of injury. The attitude of the profession should be one of the utmost conservatism.

Methods for the Therapeutic Employment of the Different Tuberculins.

Combe (Le Nourrisson, v. Jan., 1917, from Jour. Amer. Med. Assoc.) advocates a systematic tuberculin treatment of **tuberculosis in infants**. If the dose injected subcutaneously is adapted to the assimilating power, there is a general immunizing reaction in addition to a focal cicatrization reaction. Excessive dosage induces anaphylaxis. He begins with $\frac{1}{10}$ milligram and increases the dose gradually at 3-day intervals, up to 0.1 or even 0.5 Gm., testing the results with intradermal injection of always $\frac{1}{10}$ milligram every 2 weeks. The progressive diminution of the reaction to this Mantoux intradermal test, while the therapeutic dose is being constantly increased shows that immunization is effected. If the Mantoux reaction grows more pronounced, the tuberculin should be suspended.

To determine the exact dose of tuberculin for pulmonary **tuberculosis in children**, Myer Solis-Cohen (Trans. Am. Med. Assoc.; N. Y. Med. Jour., June 16, 1917) injects intracutaneously in 1 forearm, distally, medially, and

proximately, respectively, 0.0000001, 0.000001, and 0.00001 milligram. If no reaction occurs, he later injects in the other forearm 0.0001, 0.001, and 0.01 milligram, and so on, up to 10 milligrams. The smallest amount producing a reaction is then given therapeutically *per os* or hypodermically. One patient reacted to 0.0000001 milligram, another to 10 milligrams, a dose a hundred million times larger.

P. H. Ringer (So. Med. Jour., Feb., 1918) urges the following as fundamental facts in connection with the administration of tuberculin: Tuberculin must never be looked upon as other than an aid in the treatment of tuberculosis; must never be accorded first place, and must never be allowed to supplant, but only to supplement a strict dietetic-hygienic regime. It must not be used by the inexperienced, as in their hands much harm will result. It must be used in a restricted number of cases, and a good reason for using it must be present, a reason other and better than the mere fact that the patient has tuberculosis.

The dose of tuberculin must not be regulated by rule of thumb, but must be highly individualized. While opinions differ on this point, Ringer believes that in the long run the optimum and not the maximum dose should be sought, as it is a well known fact that a large amount of tuberculin tolerance is not synonymous with the establishment of a high grade of immunity to tuberculosis.

Users of tuberculin must be on terms of intimacy with the physical signs presented by their tuberculin patients, and they must be familiar with the early signs of activity in the lung, whether of recent or recurrent origin. They must auscultate their tuberculin pa-

tients before, practically, every dose, as only by so doing will mild focal reactions be recognized and dose governed accordingly. They must have before them a definite conception of what tuberculin can do, of its mode of operation, and of what is desired in each particular case.

Ladron de Guevara (*La Cronica med.*, Mar. 25, 1917) gives the **indications** for tuberculin therapy as follows: recent onset with slight involvement, general good condition, and normal temperature; latent or larval forms; slowly advancing cases of bilateral disease which have improved under general hygienic treatment; chronic fibrocaseous phthisis. Contraindications are acute cases; extensive involvement with poor general condition; cases with multiple visceral foci; tachycardia above 120; mixed infections; high fever; and cardiac lesions.

Dangers and Limitation.—One of our ablest phthisiologists, Dr. Baldwin (*Therap. Gaz.*, Mar. 15, 1918), an associate of the late Dr. Trudeau, of Saranac Lake, concludes as follows: Tuberculin is one of the most mysterious medicinal agents used in tuberculosis. It has such a powerful, explosive effect at times, which is fraught with danger, that no little study should be devoted to its action by physicians who use it. It is regrettable that few acquire such knowledge before embarking on the experiment. The consequences of such superficial conceptions as may be prevalent are two-fold: either the tuberculin is used too timidly, or too recklessly. In both cases the patient really fails to get a fair deal. The first method has the merit of safety, but normal saline might accomplish as much. The second involves danger of harmful reactions, depressing to the

patient and likely to aggravate the disease, more especially lung tuberculosis.

Tuberculin is an agent of limited application with safety when employed in *quiescent* pulmonary tuberculosis. It is not immunizing in the sense that relapse is prevented, although it may diminish the number of febrile exacerbations during the course of the disease. It is contraindicated in active, progressive pulmonary tuberculosis. It can be used with benefit in reacting doses for certain localized or circumscribed tuberculosis.

G. E. Bushnell (*Military Surg.*, June, 1918) states that he has too often seen very serious harm from tuberculin, as employed by others, to be enthusiastic concerning its use. Tuberculin is most helpful to those who need help least. Advanced cases of tuberculosis are very seriously injured by it, but the rather numerous class of sanatorium patients who have little or no active tuberculosis, their disease being of a chronic, though often diagnosticated as acute type, are able to tolerate it, sometimes apparently to their advantage.

Administration by Mouth.—Latham, Spitta, and Inman (1908) ascertained the value of vaccines and tuberculin administered by the mouth. They have tried these substances given in normal saline solution and in fresh horse serum. The doses of the vaccine, when administered by mouth, should be slightly larger. Apparently the negative and positive phases which follow the administration of vaccines by the mouth are shorter than those produced by the hypodermic method. The tuberculin used was T. R.

S. Solis-Cohen, of Philadelphia, after two years' investigation of the use of tuberculin by mouth, has confirmed the observation of Latham and his co-

workers. In a signed editorial appearing in the *New York Medical Journal* (p. 132, January 20, 1912), the author states that he finds diluted milk whey and physiological saline solution equally as valuable as the horse serum recommended by Latham as a diluent for the tuberculin. He employed a sugar of milk trituration and directed that the dose should be taken at bedtime. His results confirmed Latham's observation that distinct reactions may occur from very small doses ($\frac{1}{100000}$ mg.). The author states that there is an advantage in administering the dose early in the morning so that the time of the oncoming of reaction can be more readily observed and charted; but, on the other hand, the fact that a mild reaction may be sustained in sleep has also some advantages. Attention is called to the general rules of minimal doses progressively increased, with absolute rest during reaction time, which must be observed in this as in all other methods of using tuberculin. He begins with $\frac{1}{100000}$ mg. of T. R. rubbed up with 1 Gm. of milk-sugar, and increases the dose by $\frac{1}{100000}$ mg. until a reaction is evident. One dose is given every third or fourth day unless for some good reason, as prolongation of temperature rise, or excessive local or general reaction, its omission is necessary. After a reaction is evident, no increase of dose is made until the reaction-inducing dose has been twice repeated without causing rise of temperature. The maximum limit is fixed by the necessities of the case. Usually from $\frac{3}{10000}$ to $\frac{1}{1000}$ mg. is required. The author uses a highly nitrogenous and moderately fatty dietary, together with such medication as is indicated in connection with the gastric administration of the tuberculin.

Localized Tuberculosis.—In connection with the treatment of cases of strictly localized tuberculous infection, we must take into account the following facts:—

1. The tuberculo-opsonic power of the blood in infected persons appears to be uniformly inferior to that of normal blood.

2. The immunizing stimuli which are required for raising the opsonic power and for maintaining it at a high level are lacking.

3. The tubercle bacilli are cultivating themselves in the focus of infection under favorable conditions.

4. An increase of the opsonic power can be obtained and maintained by the inoculation of a series of properly adjusted and interspaced doses of tubercle vaccine.

Wright classifies the cases of local tuberculosis which have derived benefit from vaccine therapy under the headings of lupus, tuberculous ulcers of the subcutaneous tissues, tuberculosis of the bone, tuberculous glands, tuberculous diseases of the genitourinary system, tuberculous diseases of the joints, tuberculous peritonitis, and apyrexial phthisis.

In treating **lupus**, not infrequently certain of the patches are seen completely cured, while the disease in other regions remains refractory. These only partially successful results which contrast in a very unfavorable manner with those obtained in connection with tuberculous ulcerations affecting the deeper tissues seem to depend not so much upon a defective power of response to inoculation on the part of the patient as upon the inadequate manner in which the antibacterial substances come into application upon the tubercle bacilli in the skin, which is but poorly

supplied with blood. If it were possible to superadd to the treatment by inoculation another form of treatment which achieves, as, for example, the Finsen light, a sufficient transudation of lymph into the skin, the efficiency would be much greater.

In tuberculous ulcerations of the subcutaneous tissues the results from tuberculin therapy have invariably been satisfactory when given with proper precautions. Tuberculous lesions of the **lymphatic glands** seem especially favorable for treatment by tubercle vaccine, as those glands lie in the direct course of the lymph-stream.

Tuberculin has a decided curative effect in all cases of **tuberculous adenitis**, according to A. R. Allen (Penna. Med. Jour., Dec., 1912). There is a marked increase in the weight and improvement in the general health. Where discharging sinuses are present they close promptly, and wounds remaining from broken down glands heal kindly and rapidly.

At the Westfield State Sanatorium, Mass., according to H. D. Chadwick (Boston Med. and Surg. Jour., Jan. 7, 1915), patients having **cervical tuberculous adenitis** and showing no more than 1 degree of temperature, and no other signs of active pulmonary disease, are given tuberculin treatment, the bacillin-emulsion being used. The initial dose is one millionth of a milligram and the course of treatment extends over a period of about 6 months until the maximum of 10 milligrams is reached. The glands decrease perceptibly in size and the area of dullness over the hilus becomes less pronounced. Surgical interference is necessary to remove only such glands as have become caseous or fibroid.

Vaccination Against Tuberculosis.

—The question of vaccination against tuberculosis has been interestingly discussed by Calmette (Rev., March 30, 1912):—

"Calmette states that none of the methods hitherto in vogue has succeeded in inducing the formation of the durable vaccinating lymph-node lesion which seems to be indispensable for resistance to true tuberculosis later. He revives them all and compares them unfavorably with the results of his recent vaccination work on cattle which opens brighter prospects. He regards as almost inevitable the contamination of children under 5 with tuberculosis, at least in crowded cities. If this infection remains localized in the lymph-node system—which it generally does—and if the infection is not massive, it confers on the child an immunity to reinfection or at least makes it more resistant, so that re infecting bacilli are not tolerated; the organism then displays a characteristic tendency to dispel them at once, while it displays an equally characteristic intolerance for the products of the bacillary secretion (reaction to tuberculin). This resisting power can be measured by quantitative determination of antibodies in the serum. The antibody index shows that the resistance increases with each new infection manifested by the greater and greater tendency to rapid cheesy changes, purulent softening of tubercles and prompt expulsion of their contents. But when infection recurs again and again and in massive doses, this constant recurrence of softening and breaking down of tubercles overwhelms the system with their prod-

ucts, brings on the condition of actual phthisis, and the individual finishes by succumbing in spite of or rather for the very reason that he has acquired immunity. These facts point the way to effectual prophylaxis, Calmette thinks. As soon as the tuberculin first reveals that infection has occurred, the child is protected against reinfection; he has acquired immunity and resisting power enough to carry him through life if he can be protected against massive reinfections. Calmette adds that it is possible to conceive of artificially inducing this primary immunizing lymph-node action by vaccination in very young infants, by feeding them some attenuated strain of tubercle bacillus while the intestinal walls are still in their primal comparatively permeable condition."

Bertarelli (*Gaz. degli ospedali*, Sept. 6, 1917) tried tuberculin on himself, and found that the deviation of complement test elicited a positive reaction in a few weeks after he had begun to give himself a weekly injection of minute amounts of old tuberculin. By the end of a year he had reached the dose of 1 c.c., and now, three years after the last injection the deviation of complement test is still strongly positive. Theoretically, a prophylactic course of tuberculin would seem justified in families exposed to special danger of infection, and he urges others with more opportunity to try it.

Mixed Infections in Tuberculosis.—Investigations show that at least 75 per cent. of cases of pulmonary tuberculosis are due to a mixed infection. A rapid decline in the patient's condition is the usual clinical indication. Streptococci, staphylococci, influenza

bacilli, and the pneumococci are frequent offenders. It stands to reason that the clinical symptoms manifested in such cases cannot be characteristic of any one invading organism, but that they must be the symptoms of a composite toxemia. Unless the patient so affected is able to elaborate sufficient antibodies he is in constant danger of further attacks or relapses. Often his condition becomes chronic. The chronicity can be explained by the fact that the patient's resistance is sufficient to hold the infection in abatement, but insufficient to overcome it. Such cases seem to offer a wide field for vaccine therapy and possibly autogenous vaccines afford more direct and positive means of combating the infections than stock vaccines.

Vaccination against the secondary infections will by no means remove all symptoms. However, an approximate improvement can be expected. When this improvement reaches a stage where the symptoms seem to be produced almost entirely by the tuberculous processes, tuberculin treatment would seem indicated and should then afford marked improvement. We must, of course, always keep in mind that hygienic treatment is a necessary accessory.

The stage of hectic tuberculosis, Huguenin remarks, has long been known to be related to a mixed infection. Ziegler, in his "Pathological Anatomy," 1st ed., has mentioned it; Holst, 1888 (*Norsk. Mag. f. Lag.*), also, upon finding streptococcus in lungs, spleen, and kidneys in pulmonary tuberculosis, states that the last stage is a kind of pyemia. Others reached the same conclusions as to the

peculiar course of chronic pulmonary tuberculosis. The rôle of mixed or secondary infection was long known in other infectious diseases (*e.g.*, croupous pneumonia, typhoid, and acute exanthemata) before the analogy was applied to pulmonary tuberculosis. This was due to the fact that many believed in the power of the tubercle bacillus to cause true suppuration. Huguenin, however, believes with Rosenbach, Garre, and others: "When true suppuration is present in tuberculosis it is conditioned by the primary presence of the secondary immigration of pyogenic bacteria." In the lung there is a symbiosis of bacteria of different kinds to which the fever is to be ascribed. The question is whether the fever is due to the assimilation products and body contents of the tubercle bacillus, to the tuberculin alone, to the analogous products of the pus cocci, or to a new material formed from both together.

Leigh and Tint (Ill. Med. Jour., 1912) have had favorable results from the use of autogenous vaccines. They state that repeated careful examination of sputum in advanced and moderately advanced cases of pulmonary tuberculosis before or after a hemorrhage reveals the constant presence of the pneumococcus, streptococcus, *Micrococcus tetragenus* and *Micrococcus catarrhalis* in addition to the tubercle bacillus. During a hemorrhage pneumococci were sometimes the only organisms found. Low opsonic indices to the pneumococcus and streptococcus in pleurisy and the constant presence of either of these organisms in pyopneumothorax suggested the application of autogenous vaccines in order to miti-

gate some of the symptoms of tuberculosis.

The cases treated are divided into three groups:—

First.—Incipient pulmonary tuberculosis with night-sweats; frequent unproductive coughing, with positive von Pirquet reactions and no tubercle bacilli in the sputum.

Second.—Advanced pulmonary tuberculosis.

Third.—Cases with cavity formation in one or both lungs and accompanied by frequent hemorrhages. For the preparation of the vaccine the sputum was collected with great care and after washing in saline solution isolations were made on glucose-agar, blood-agar, and blood-serum. The initial dose of the vaccine was 50 million if a single organism was found, or a mixture containing about this number. The dose was doubled weekly until 200 million was reached. Following the injection of the vaccine there was local hyperemia and tenderness at the place of injection. Clinically the cough became productive in a few days and the mucopurulent expectoration was replaced by a more watery material, which was expectorated easily. Respirations became less labored and wheezy, grew easier, and gradually became normal. Night-sweats ceased, the appetite improved, patients gained in weight, and they rested altogether more comfortably. In the far-advanced cases with cavity formation the distressing symptoms did not entirely cease, but there was some relief. In all, 50 cases were studied: 20 incipient, 22 advanced, and 8 far advanced.

LEPROSY.

Rost (Ind. Med. Gaz., vol. xlv, pp. 249-253, July, 1911) gives a clinical

report of the treatment of leprosy by the use of a bacterial vaccine prepared from cultivations of the leprosy streptothrix. This report includes 12 cases. They were all voluntary cases and not chosen ones. Five of them are now practically cured as far as clinical observation goes, and the others are all remarkably improved. The vaccine was injected weekly and temperature records taken, almost always showing a rise of temperature varying from 100° to 105° F. The writer is inclined to believe that the best vaccine is a sterilized six weeks' broth culture. His doses have been 1 c.c. of a 1:400 dilution of dried culture and 1 c.c. of a sterilized six weeks' broth culture. It is advisable to obtain only slight reactions in nodular cases, whereas in anesthetic cases the greater the reaction the better the result. The reason for this probably lies in the fact that in the anesthetic form the bacilli are situated in the nerves, and there is no danger of metastasis as there is in the cases with large nodules.

DIPHTHERIA.

The very satisfactory results attending the therapeutic use of diphtheria antitoxin have probably retarded the development of measures for the production of active immunity. It would seem, however, when we consider the rapidly spreading nature of epidemics, especially in institutions, that a more satisfactory prophylactic agent than antitoxin should be found. While antitoxin does confer a satisfactory state of immunity, the greatly exaggerated danger of anaphylaxis makes many physicians hesitate to use it; and since it confers only passive immunity the refractory state is probably very short. Anti-

toxic immunity in certain instances lasts not more than a week, although it may exist for a much longer period in certain individuals. Some very interesting work has been done along the line of *active immunity*, but methods have not been made so practical that they have been used to any extent by the medical profession.

In 1903 William H. Park, Director of the Laboratory of the Board of Health, New York, showed that animals could be actively immunized with neutralized mixtures of toxin and antitoxin. In 1915 (Boston Med. and Surg. Jour., Aug. 26, 1915) the same investigator recalling the fact that, 1000 units of antitoxin will confer immunity for about 3 weeks, this short duration led to efforts to increase it. Behring used a toxin-antitoxin mixture for this purpose. Theobald Smith having previously shown that it speeded and increased the antitoxin yield of horses. Individuals deprived of natural immunity were with great difficulty found to be made immune however, while 25 per cent. of the natural non-immunes could not be made immune at all. For practical purposes, therefore, passive immunity remained the chief measure. Bacterial vaccines had virtually failed to give immunity. He therefore, concluded that future efforts should aim to combine toxin-antitoxin and vaccine therapy to increase both antitoxic immunity and anti-body immunity.

In a paper before the New York Academy of Medicine, three years later (New York Med. Jour., Aug. 3, 1918) Park gave the results of the intervening period which briefly showed not only the possibility, but the feasibility of immunizing the child population against diphtheria.

The injections, he said, were per-

fectly harmless. The tests were carried out on children in institutions. The children first were given the Schick test (see below) and then immunized. It had been possible to check up the results, and up to the present there had been no untoward consequences. Some showed a reaction, but in none were there any after-effects. There had been no cases in which any harm had resulted. The blood and urine were examined at regular intervals, but revealed no changes. There had been no local reaction beyond a slight redness and hardly appreciable swelling.

The injection was made in the arm; the amount was $\frac{1}{2}$ c.c. in infants, $\frac{2}{3}$ c.c. in those 1 year old, and 1 c.c. in older children. Recently, 1 c.c. had been given even to infants, as there had been no bad after-effects.

If the injections could be given combined in one amount, this would simplify the process, and experiments were being made along this line, with a view to giving 2 or 3 c.c. in scattered regions. At present it was found that 3 injections gave immunity in 98 per cent., 2 injections in 90 per cent., and 1 injection in 75 per cent. Most of the work had been done with 3 injections.

As to the time, it had been found that no immunity developed for 2 weeks, but from the second to the fourth or fifth week there was rapid increase in the number that were immune. In the fifth week three fourths were immune, and in 2 months all were immune. All the immunity was tested by the Schick reaction, and there was in addition the result that no diphtheria had followed in the immune cases. In a home for infants, where this immunity had been produced, they had had no diphtheria for 2 years.

At birth a child had a positive im-

munity transferred by the mother but this generally disappeared during the second 6 months of life, though in some, not until the end of the second year. Therefore one could not depend on a negative Schick as an indication of permanent natural immunity until this time. If after 4 years of age the child was immune, it was so through the production of the child's own cells, and the immunity was permanent. This brought up the difficulty of knowing what to do in immunizing infants. They could all be immunized without regard to the Schick reaction, and that was probably the best way except in institutions where regular tests could be made and any change from negative to positive instantly noted and acted upon. Outside of institutions it was best to immunize all children whether immune or not, and a retest should be made in 6 months or a year of all those that reacted. It depended on the family and the circumstances, but whether the child was immune or not during its first year, 3 injections would give active immunity, though a little less would develop in those already immune than in those susceptible.

Park deemed it essential to immunize the infant and not the schoolchild. The statistics of death in New York City from diphtheria in 1917 showed 133 in the first 12 months, mostly from 2 to 6 months; 274 in the second year, 186 in the third year, 152 in the fourth year, and 97 in the fifth year. At the primary school age there were only 20 per cent. that were not immune, but when one thought of the deaths that occurred before school age, the necessity for conferring immunity was very apparent. The immunity thus induced in infants lasted probably for life, for once having been instituted, it was con-

tinued as a natural immunity. It was a question whether the amount of diphtheria warranted the trouble of giving the injections, but on the part of the infant and the parents there was no objection; there was no wound and no discomfort like that of vaccination for smallpox. The department of health urged upon the general population the consideration of the value of this immunity.

Zingher (Jour. Infect. Dis., Nov., '17) divides the indications into 2 groups: (a) as a general prophylactic measure, and (b) to control outbreaks of diphtheria. It is a safe and convenient rule to follow to immunize with toxin-antitoxin all children below 18 months of age irrespective of the Schick test they may show at the time of immunization. The immunity developing from toxin-antitoxin is slow in appearing, and is, therefore, not a reliable safeguard in hospital wards where children are crowded together, and suffering from various contagious diseases. But in institutions where small outbreaks of diphtheria have occurred, or where diphtheria is more or less constantly present and clinical cases and bacillus carriers steadily appear, Zingher says, the use of antitoxin alone has often been insufficient to stamp out the disease.

A. F. Hess stated (N. Y. Med. Jour., Aug. 10, 1918) that at the Hebrew Asylum the children given a positive Schick test were immunized by toxin antitoxin injection. There had been no cases of diphtheria in the institution in the last 2 years. At first all cases giving a positive Schick test were immunized, but babies were found to be immune at first and then lose their immunity; thus it would seem best to immunize all individuals during the

first 6 months of life in order to render the institution free of diphtheria.

The persistence of immunity following toxin-antitoxin injections, as observed by Park (Proc. Soc. for Exper. Biol. and Med., Apr. 8, 1918), is as follows: Adults and infants under 6 months are immune to 80 per cent., while very young children are non-immune to about 60 per cent. In adults and infants under 6 months are immune to 80 per cent., while very young children are non-immune to about 60 per cent. In infants 2 years after successful immunization the great majority have remained immune, not over 6 per cent. losing their immunity. We have a right therefore to hope that the stimulated immunity has been replaced in the very great majority by a natural immunity, and that this will hold for life. The facts that the protection lasts and that the injections are harmless make the active immunization of infants appear to be a practical measure of eliminating diphtheria.

SCHICK TEST.—Schick described in 1913 a method by which the susceptibility of an individual to diphtheria may be ascertained. He injects a small amount of diphtheria toxin ($\frac{1}{60}$ of the minimum lethal dose for a guinea-pig weighing 300 grams). This is so diluted that it is contained in 0.1 mil of fluid. In the subject tested this should be injected with a very small needle, taking care that it goes directly into the skin, the flexor surface of the forearm being the chosen locality. A *small, raised, white-looking area* should result. Within 24 hours this area becomes *somewhat cyanotic, slightly edematous and reddened*. In 48 hours this passes off and a *brownish pigmentation follows*. This reaction occurs only in persons without natural antitoxin in their blood, and if such a reaction is positive, it indicates that less than $\frac{1}{60}$ of a unit of antitoxin is contained in 1 mil of blood, and the person may be considered susceptible to

diphtheria. Children sick with diphtheria give the reaction when tested before having received the antitoxin serum. The newly born rarely give the reaction; they are usually immune (93 per cent.).

According to Zingher (*Amer. Jour. of Dis. of Child.*, Apr., 1916) from 17 to 32 per cent. between the ages of 2 and 16 years give a positive reaction.

Summarizing their results W. H. Park and A. Zingher (*Trans. Amer. Assoc. of Immunol.*; *Jour. Amer. Med. Assoc.*, July 8, 1916) conclude that it is advisable to immunize children soon after the first year of life, giving protection at a time when the disease is most dangerous. In addition, such children show only mild local and constitutional symptoms after the injections. An immune child population could thus be developed, and the bacillus carrier would probably soon disappear.

Koplik and Unger (*Jour. Amer. Med. Assoc.*, Apr. 15, 1916) enumerate several disadvantages in the Schick test as usually carried out, including technical difficulties and a considerable proportion of pseudopositive reactions. They have devised a needle, bent to an angle of 170° one-quarter inch from its point, and mounted so as to leave exposed only the portion distal to the bend. This needle, when dipped into pure diphtheria toxin, and immediately thrust endodermally, carries with it an almost immeasurable amount of fluid—about 0.00014 c.c. Parallel observations were made with this simplified technique and the accepted Schick technique, and with perfect concordance as result. Traumatic pseudopositive reactions were entirely absent, and three-quarters of the pseudopositive reactions were eliminated.

Treatment.—Vaccine treatment of diphtheria can be applicable only to the chronic conditions associated with diphtheritic rhinitis or unusual infections in various other parts of the body. The acute condition is so promptly and positively relieved by antitoxin that except in asthmatics and other persons known to be hyper-

susceptible to horse serum no other form of treatment is to be considered.

Bosanquet and Eyre (*"Serums, Vaccines, and Toxins,"* Funk and Wagnalls, N. Y., p. 107, 1910) say that vaccine treatment is of distinct value in those infections which become chronic and in which the responsible organism remains domiciled in the throat or nose for long periods after the acute symptoms have been entirely removed by the use of antitoxin. A vaccine may be prepared from the strain of the diphtheria bacillus actually infecting the patient and administered in doses of 5 to 10 million at intervals of five to seven days. One or 2 injections are usually sufficient to insure the disappearance of the bacilli from the local site of infection.

Forbes and Newsholme (*Lancet*, vol. i, No. 5, p. 292, Feb. 3, 1912) report the treatment of patients with **membranous rhinitis** by autogenous vaccines. They give in detail the treatment of 3 patients; the intervals between doses were five to seven days. Treatment was started in 2 of the cases on Nov. 9th with 5 million diphtheria bacilli. Subsequent doses were 10, 40, 80, 100, and 200, and the last dose on Dec. 20th was 400 million. In these 2 cases bacilli persisted in the nose even after this final dose, but the membrane had cleared up and only the nasal catarrh remained. In one of the cases the local condition seemed to be entirely cleared up by the injections. The swabs in all cases before treatment showed almost pure cultures of diphtheria bacilli, but after treatment they were scanty and mixed with other organisms.

Koepe (Zeit. f. Kinderheilk., vii. Nu. 1-2, 1913) has noticed that in giving von Pirquet's test the enlarged axillary glands on the side of the test frequently decreased in size, while those on the other side were unmodified. He concluded that the tuberculin, entering the lymph-spaces, was carried to the lymph-nodes, where it exerted a direct curative effect. Four were treated in the same way since, with good results, and he recommends it as a therapeutic measure in all cases where the lymph-nodes are swollen and hard and the Pirquet reaction is strongly positive.

Diphtheria-bacillus Carriers.—

Among the most troublesome conditions the health officer has to deal with is the persistence of diphtheria bacilli in the throats of persons after recovery from the disease. Typical bacilli remain in and upon the tonsils sometimes for months. Such persons must be considered a menace to the community and held in quarantine. An efficient and practical method for clearing up such conditions is highly desirable. Vaccine treatment has been tried, and with a measure of success, but failure to rid finally and effectively the focus of infection of the causative organisms seems to be one of the chief limitations of vaccine therapy. As in colon-bacillus cystitis, the symptoms may be entirely relieved and the patient symptomatically cured while colon bacilli are still present in the urine. Vaccine treatment, for this reason, has not been so uniformly successful as to make it the universal method.

Walton-Smith (Australasian Med. Gaz., vol. xxix, pp. 543-4, Oct. 20, 1910) reports the treatment of a diphtheria-bacillus carrier of three months'

standing with a mixed vaccine composed of diphtheria bacilli and staphylococci. The writer does not state whether the staphylococcus was albus or aureus. In view of the interesting work recently reported by Schiotz, Page, and others, it would be interesting to learn whether the staphylococcus was aureus or not. After 2 doses of the vaccine, the throat cleared up.

A method of utilizing the antagonisms which exist between bacteria of different kinds has been suggested by Schiotz (Ugesk. f. Laeger, 71, p. 137, 1909; abs. from Jour. Amer. Med. Assoc., 54, p. 442, 1910). He was much impressed with the fact that a patient with staphylococcus sore throat placed in the diphtheria ward by mistake had not contracted diphtheria, and also with the fact that intercurrent attacks of staphylococcus sore throat in several cases terminated positive diphtheria-bacillus findings in cases convalescent from diphtheria. Acting on the presumption that the staphylococcus was responsible for the immunity on the one hand and of the cure on the other, he inoculated altogether 6 diphtheria carriers with staphylococci, with complete success in each instance.

Page (Arch. Int. Med., vol. vii, 1911) has called attention to the method of Schiotz, reporting the use of *Staphylococcus pyogenes aureus* in a patient. He sprayed the throat with a pure culture of the *Staphylococcus pyogenes aureus* and found that the diphtheria bacilli disappeared within forty-eight to seventy-two hours.

Catlin, Scott, and Day (Jour. Amer. Med. Assoc., vol. lvii, No. 18, pp. 1452-3, Oct. 28, 1911), acting upon the advice of Harris, made use of a spray of broth culture of the *Staphylococcus*

pyogenes aureus in 8 diphtheria carriers. A twenty-four-hour culture was sprayed into the nose and throat two or three times daily, all other treatment being stopped. In no instance did any harmful condition develop as a result of the introduction of the staphylococci. Two persistent carriers failed to give a single positive diphtheria culture after the first application of the staphylococci. One person had 1 positive culture after using the spray and 1 other had 3 positive cultures. One nurse was persistently positive, and it was discovered that she had avoided using the spray as directed. More careful trial of the treatment immediately cleared her throat of all diphtheria organisms. As serious infections of the nose and throat are caused exclusively by the staphylococcus, until we know more about such things it would seem that sprays of living staphylococci should be used only with the co-operation of a bacteriologist.

Labbé and Canat (Paris méd., Jan. 6, 1917) report very favorable results from insufflation of a powder made from the serum of horses previously injected with diphtheria bacilli killed by heat. This powder was insufflated into each nostril of the diphtheria carriers 4 times a day. One teaspoonful of the powder in the atomizer bottle serves for 30 insufflations.

ACUTE AND CHRONIC INFECTIONS OF THE RESPIRATORY PASSAGES.

Their location and function render the mucous membranes of the respiratory passages the most exposed tissues of the body. All air-borne organisms as well as those carried in food and other material taken in the mouth may come into direct contact with these

membranes, often finding lodgment there and the chance for development. Considering the constant exposure of these tissues severe infections are very rare and under ordinary circumstances they must possess a high degree of local immunity. When for any reason vascular disturbances ensue or more profound pathological changes exist, it is not surprising that bacteria do develop. The most common infection is a catarrhal condition commonly known as "cold." The great importance of the different types of bacteria in this relation has naturally led to a study of the bacterial flora in the nose, mouth, and throat in health and disease. The results of these studies have been utilized recently for therapeutic purposes in treating various inflammations of the respiratory passages with bacterial vaccines. The bacteria which have been found most frequently are the staphylococci, streptococci, pneumococci, *Micrococcus catarrhalis*, *Bacillus influenzae*, bacillus of Friedländer, and various organisms morphologically resembling the diphtheria bacillus. The diphtheria bacillus, to be sure, is found in the course of the disease caused by it, as are other parasitic bacteria during their specific manifestations.

English writers are very fond of referring to the *Micrococcus paratetragenus* and the *Bacillus septus* or *Bacillus coryzae segmentosus*. The *Bacillus paratetragenus* was described by Bezançon and De Jong (Bull. et Mém. Soc. Méd. Hôp. de Paris, vol. xxii, 3d ed., pp. 165-169, 1905). In the examination of a large number of specimens collected in and about Philadelphia this organism has not been found.

Allen has paid more attention to

the treatment of common colds by bacterial vaccines than probably anybody else. According to his experience it is advisable for purposes of immunization to use a mixed vaccine. He has successfully treated patients with colds caused by one of the catarrhal organisms only to find that a little later another cold developed, caused by another member of this group.

Vaccines are held by some specific. According to J. W. Fisher (Boston Med. and Surg. Jour., June 5, 1913), an immunity may be obtained lasting on the average, from 4 to 6 months. In those subject to recurrent colds in winter an autogenous vaccine should be made from the first cold, to which may be added other stock "cold germs": staphylococcus, 400 to 800 million as the full dose; pneumococcus, *M. catarrhalis*, and *M. tetragenus*, of each 125 million; *B. influenza*, *B. septus*, and *B. Friedländer*, of each 100 million; and streptococcus, 50 million. Eight minims (0.5 c.c.) of the vaccine should contain the required number of sterile germs. The vaccine is given in increasing dosage at weekly intervals until four to six doses have been administered.

R. H. Babcock (N. Y. Med. Jour., Jan. 8, 1916) used autogenous vaccines prepared from the sputa. It yielded results in 3 cases of **acute bronchitis**, 1 of chronic bronchitis, and 4 of **chronic bronchitis** associated with attacks of spasmodic asthma, as to warrant him in recommending this mode of therapy in preference to the old time use of expectorants by mouth. The main drawback is the necessity of several cultures and the preparation of new vaccines, should the cultures show that some of the originally found germs have dis-

appeared or become subordinate in number to others. New vaccines should be prepared whenever the condition of the patient seems to have come to a standstill. Great care is necessary in avoiding too large doses lest a negative reaction occur.

H. A. Cables (Lancet-Clinic, July 22, 1916) lays stress on the efficacy of vaccine treatment. He uses stock vaccines of the Van Cott formula. The first dose given is a large one, to excite the formation of a great amount of antibodies. The interval between doses is always at least 4 days, and is lengthened to a week or 10 days as improvement takes place. Codeine, $\frac{1}{4}$ grain (0.016 Gm.) every 2 hours, is often given to procure temporary relief before the action of the vaccine is brought into play. A typical dose of vaccine contains 50 million streptococci, 100 million each of colon bacilli and pneumococci, and 500 million staphylococci. The improvement following each dose depends upon the severity of the reaction, which is partly local and partly systemic. Great care is taken to eliminate cases of tuberculous infection.

Treatment of **influenza** by bacterial vaccines offers some hope of success. From the work done by Wright, Allen, Synnott, and others, positive results are obtained by injections of a vaccine repeated at short intervals. It is to be remembered that even in the course of an epidemic of influenza not every condition diagnosed as grip is caused by the influenza bacillus; furthermore, in many cases in which the influenza bacillus is involved it is not the only pathogenic factor. For the treatment of influenza, then, especially after the disease has existed for a longer time than a very few days, a mixed vaccine is indicated. The physi-

cian may not expect to control the many unfortunate sequels of this condition if a vaccine containing only the influenza bacillus is used.

In a study of the etiological relationship between common colds, and influenza, Hitchens (Med. Rec., Feb. 17, 1912) states that the omnipresence of the "cold" bacteria promotes the formation of antibodies. These functions being temporarily arrested or hampered by external physical conditions or by the attacks of more virulent bacteria,

cold organisms may be the guilty one, and in most cases of cold at least several varieties are concerned. Hitchens, therefore, advocated for general use a mixed influenza vaccine. As at present dispensed, (1919) four graded strengths are available in as many aseptic glass syringes ready for use for the prophylaxis and treatment of common colds, mixed infections of the respiratory mucosa and influenza. The composition and activity of each syringe are as follows:—

Syringes	A	B	C	D
Bacillus influenzae	12.5	25	50	100 million per c.c.
Staphylococcus aureus	50	100	200	400 million per c.c.
Staphylococcus albus	50	100	200	400 million per c.c.
Streptococcus	12.5	25	50	100 million per c.c.
Pneumococcus	12.5	25	50	100 million per c.c.
B. Friedländer	12.5	25	50	100 million per c.c.
M. catarrhalis (group)	12.5	25	50	100 million per c.c.

the treatment indicated is one capable of stimulating the formation of antibodies by the use of bacterial vaccines.

One of the first conditions treated on these principles was what he deemed to be a type of "cold," influenza. The results were encouraging, but the plan of isolating the most active agent and using the corresponding bacterial vaccine soon began to show its inadequacy. A patient treated with pneumococcic vaccine remained as susceptible as ever to the influenza bacillus, micrococcus catarrhalis group, etc., and for both prophylactic and therapeutic purposes a vaccine composed of all the "cold" organisms was employed. Thus, if the influenza bacillus is the chief offender, while stimulating the production of antibodies against this micro-organism the immunity against the other varieties and thus preventing a second attack by one of them is also enhanced. On the other hand, it is difficult and in many cases impossible to tell which of the

In chronic conditions and for immunization the contents of syringe A may be injected and in 5 days the contents of syringe B. Again in 5 days the contents of syringe C, and the contents of syringe D in another 5 days. If marked local or constitutional reaction follows, the subsequent dose must not be increased. The same dose may be obtained by injecting one-half the contents of the next syringe in the series.

In acute conditions the initial dose may be one-half the contents of syringe A, following with the remainder in from 3 to 5 days, and continuing with B, C, and D, according to indications, in the same general manner as for prophylaxis.

C. H. Duncan (Med. Standard, Mar., 1916) asserts that autotherapy usually cures acute influenza in twenty-four hours if the following simple technique is properly employed: Mix sputum 1 dram (4 c.c.), distilled water 1 ounce (30 c.c.), in a 2 ounce (60 c.c.) bottle,

shake well, and allow to stand twenty-four hours. Filter through a Berkefeld filter. Inject 20 minims (1.25 c.c.) of the bacteria-free filtrate into the loose cellular tissue over the biceps muscle. Give no further dose until the patient ceases to improve under the preceding dose.

Three strains of influenza bacilli obtained from cases during the epidemic were used by Leary (*Amer. Jour. of Public Health*, Oct., 1918) in the preparation of a vaccine. The prophylactic dose was 0.5 c.c., 1 c.c., and 1.5 c.c. in 3 doses at 24-hour intervals. The therapeutic dosage was 0.5 c.c. every 12 hours. The author believes that all of these doses were too small, notably the therapeutic dose. The percentage of complete protection seemed high, while there was marked amelioration of symptoms in those who became ill. Pneumonia appeared in very few cases. The therapeutic use was followed by the best results when large doses were exhibited early in the disease. It should be possible to abort a large percentage of the cases, and prevent the development of pneumonia. Yet, after pneumonia has developed, large doses of vaccine produced excellent results.

Major Roberts, of the Columbia War Hospital (*Trans. N. Y. Acad. of Med.*; *Med. Record*, Nov. 2, 1918), recorded a series of cases treated with the vaccines and without. These afforded apparently conclusive evidence of the value of the intravenous vaccine treatment. In one series of 86 cases without vaccine the mortality was 35 per cent., while in a series of 153 patients treated with the vaccine the mortality was about 8 per cent. He felt sure that the mortality could be very greatly reduced by the use of the vaccines intravenously. The most striking fact

brought out by the study of these series of cases was not that the mortality was so low, but that after the first injection of the vaccines, in cases in which there had been congestion and nosebleed, the latter stopped and there was less dyspnea and very little cyanosis except in the very severe cases. The vaccines were given in 3 to 4 doses of $\frac{1}{2}$, 1, and 2 c.c., at 24-hour intervals. One c.c. of the vaccine contained 1 million influenza bacilli and 1 million pneumococci of types I, II and III, 1 million streptococci and 1 million staphylococci. He started with $\frac{1}{2}$ a c.c., and at the end of 24 hours they gave 1 c.c., and 24 hours later 2 c.c. As a rule they did not get much reaction with the $\frac{1}{2}$ c.c., though there might be a rise in temperature. Usually from the 1 c.c. dose they got a fairly definite reaction which was different from a non-specific protein reaction.

Evidence is at hand according to J. H. Kolmer (*Phila. Co. Med. Soc.*; *N. Y. Med. Jour.*, Nov. 23, 1918), indicating that the streptococcus and micrococcus catarrhalis are also concerned in the pathology of the infection, possibly not as primary agents, but as secondary factors of considerable importance. That the resistance might not be reduced, small doses of the vaccine were given at intervals of 3 days until 3 injections were given. A distinction should be made as to the practical value of commercial stock vaccine and that prepared of organisms from the present epidemic. Several thousand doses of the vaccine we have prepared have been distributed in this city. It would seem that the administration of the vaccine at intervals of 3 days does protect a certain number of persons against influenza, but it does not confer absolute immunity. Reports,

by direct correspondence from Boston, Rochester, and other cities are of a similar nature. It may, therefore, be tentatively asserted that the vaccine is worthy of trial, particularly in institutions and hospitals where a large number of people necessarily congregate.

Eyre and Lowe (Lancet, Oct. 12, 1918), during the war, tried extensively prophylactic vaccinations against catarrhal affections. The vaccine used was prepared in 2 different strengths, the weaker initial dose being followed ten days later by the second stronger dose; in each instance the volume of vaccine administered amounted to 0.5 c.c. It was prepared from organisms contained in the secretions of purulent bronchitis and in the sputums of other catarrhal cases among the troops in England. It contained:

ORGANISMS PER 0.5 C.C.

Organism.	First Dose.	Second Dose.
Pneumococcus	50	100 million
Streptococcus	10	50 million
B. influenzae	10	30 million
Staphylococcus aureus ..	200	500 million
M. catarrhalis	25	75 million
B. pneumoniae	50	100 million
B. septus	50	100 million

This vaccine was designed to produce an artificial immunity, not only against the first three virulent organisms, which are frequently found present in fatal purulent bronchitis, but also to immunize against the other organisms most frequently found in catarrhal sputums and nasal discharges.

The following results were obtained:

(a) 2081 men inoculated with the initial dose. No reaction, 2033, 97.7 per cent.; slight reaction, 42, 2.0 per cent.; severe reaction, 6, 0.3 per cent.; (b) 1627 men inoculated ten days later with the second dose. No reaction, 1607, 98.8 per cent.; slight reaction, 3,

0.7 per cent.; severe reaction, 7, 0.4 per cent. Slight reaction: headache in twenty-four cases; temperature from 99 to 101 in fourteen; sore throat in five; neck stiffness, nausea and fainting in five. Severe reaction: above symptoms more marked and accompanied by temperatures between 101 and 104. In spite of their being so small evidence of immediate reactions there was an increased susceptibility to the prevalent catarrhs of the area. These data show that the extensive use of catarrhal vaccine will not incapacitate troops in training to any appreciable extent. In order to determine whether these inoculated men had gained any appreciable immunity to respiratory catarrhal complaints, the first 1000 men inoculated, and another selected 1000 men none of whom had been inoculated with this or any other catarrhal vaccine were watched. It was found that the incidence of the influenza epidemic was appreciably less among the inoculated men than that affecting the average 1000 of the uninoculated (2 per 1000, as against 28.4 per average 1000), a result which amply justifies the prophylactic use of M. C. V.

McCoy, Murray and Teeter (Jour. Amer. Med. Assoc., Dec. 14, 1918) gave the results of strictly parallel observations made to determine the value as a prophylactic of a vaccine, each c.c. of which contained:

Influenza bacilli	500,000,000
Pneumococci, Type I	500,000,000
Pneumococci, Type II	500,000,000
Pneumococci, Type III ...	500,000,000
Pneumococci, Type IV	1,500,000,000
Streptococcus hemolytic ...	1,000,000,000
Staphylococcus aureus	500,000,000

Two or more strains of each organism were employed in the prepara-

tion of the vaccine and the doses were $\frac{1}{2}$, 1, and $1\frac{1}{2}$ c.c. respectively, at intervals of 2 days. Every alternate patient in a State insane asylum was given the vaccine, the others being untreated. Each group contained 390 persons. Inoculation was completed 11 days before the first case of influenza appeared in the institution. Of the vaccinated persons, 119 developed influenza with 23 cases of pneumonia and 10 deaths, as contrasted with 103 cases of influenza with 17 cases of pneumonia and 7 deaths among the unvaccinated.

W. F. Robertson (Brit. Med. Jour., Dec. 21, 1918) recommends, after using it in 100 cases, a vaccine made from the *Bacillus influenzae* in **chronic influenza** infections, the doses ranging from 0.005 to 0.1 mg. of the dried bacilli. Correct doses usually cause distinct focal reactions, while larger doses cause all the characteristic symptoms of an acute attack of influenza, showing the pathogenicity of this bacillus. The treatment should be continued over a period of 6 to 10 weeks. In protective inoculation other organisms must be included in the vaccine. The *Micrococcus catarrhalis* being the cause of severe, epidemic coryza predisposing to influenza, it must be included. Neither the pneumococci nor the streptococci should be included, however, for immunization, since these are purely secondary invaders. But for developed influenza a sensitized vaccine should be used, containing:

Bacillus influenzae0.01 to 0.04 mg.
Pneumococci (polyvalent) ..0.01 to 0.02 mg.
Streptococcus0.01 to 0.02 mg.
Micrococcus catarrhalis0.03 to 0.06 mg.

Bezancon and Legroux (Bull. de l'Acad. de Méd. Paris, Jan. 14, 1919)

found a polyvalent vaccine used by them, which contains in 1 c.c. 4 millions pneumococci to 2 millions each of streptococci, Pfeiffer's bacillus and *Micrococcus aureus* quite harmless. They injected daily about 0.25 c.c. at a time at first, increasing the dose to 1 c.c. In this way they injected up to a total of 13 c.c. In one group of 60 repatriated prisoners with influenza, the mortality was 8 per cent., while it was 17.8 per cent. among a group of 25 not given this treatment.

HAY FEVER.

Freeman (Lancet, pp. 814-817, Sept. 16, 1911), utilizing the theory developed practically by Dunbar in the preparation of his hay-fever serum, has attempted to treat hay fever by the production of active immunity. His method has been to collect the pollen from various grasses (although he does not think it is necessary to select different types of pollen for treating individual patients), and extract it according to Dunbar's method. Dosage has been adjusted by injecting one-third the smallest quantity that will give an ophthalmoreaction when it is dropped into the eye. There seems little doubt that there was a distinct amelioration of symptoms in the patients treated. The improvement took several forms; in some there was a greater freedom from attacks; in others the attacks were less severe and of shorter duration than in former years; the constitutional disturbances were not so great, and there was less asthma. "Those who had already developed hay fever when they commenced treatment were perhaps the most generous in their comments, possibly because they had recently had a re-

minder of what hay fever was like." Injections were given from a week to ten days apart; the larger doses were given at longer intervals, while very small doses were repeated after three or four days. When the vaccine was given prophylactically, the doses were much larger and were administered at shorter intervals in order to bring the immunity to the highest possible point. This subject is reviewed under *HYPERESTHETIC RHINITIS* in the fifth volume.

ACNE.

The etiology of acne vulgaris, which attracted only perfunctory attention for several years, has, since the use of a specific vaccine by Fleming, been the subject of widespread interest. For the treatment of acne, Wright suggested the use of a staphylococcus vaccine. This suggestion was based upon the finding of staphylococci constantly in pustular lesions, and in this form of the disease the treatment was attended with considerable success up to a certain point. Some patients were apparently cured, but many were found refractory to repeated injections; the pustular condition frequently disappeared, but comedones did not appear to be influenced. It was later shown by Fleming that these patients could be brought to complete cure by the use of a vaccine containing the specific bacillus. The doses of the vaccine generally used are from 1 to 10 million, and the injections are repeated at weekly intervals. If the staphylococcus is associated with the acne bacillus in the lesion a mixed vaccine containing the same number of acne bacilli and from 50 to 300 million staphylococci is indicated.

In 1893 Unna ("Histo-pathol. of the

Skin") described a bacillus which he believed to have a causal relationship to acne. He maintained that it was the only bacillus constantly present both in the comedo and in the pustule, but he was unable to cultivate it and drew his conclusions merely from a study of stained slides. Sabouraud (*Ann. de l'Inst. Past.*, vol. xi, p. 134, 1897; *Ann. de Dermat.*, vol. viii, p. 257; *Ibid.*, vol. x, p. 841) found the same organism, but differed from Unna in believing that pustulation in acne was frequently caused by the staphylococcus. He arrived at this conclusion from the fact that staphylococci are found in the phagocytes, while he was never able to find the acne bacillus undergoing phagocytosis; also because he was never able to produce suppuration by the subcutaneous injection of even large quantities of the acne bacillus. This is the view held at present by the majority of investigators; the acne bacillus alone is present in the deeper parts of the comedo, and staphylococci, if present at all, are confined to the superficial part and are in reality a surface contamination. Sabouraud was the first to obtain cultures of the acne bacillus. He did this by inoculating material from the lesions into a special acid medium which was incubated for a long time, thus allowing the staphylococci to die out. Another method used by Sabouraud was to place the culture in an oven at from 65° to 67° C. for several hours. This killed the cocci and left only the acne bacilli in pure culture. Smiley (*Jour. A. M. A.*, vol. lviii, No. 17, pp. 1274-1275, Apr. 27, 1912) has recently used a method with success similar to that employed by Sabouraud. Scrapings from acne lesions were heated to only 60° and for

only one hour, then daubed on a 1 per cent. oleic acid agar. Sabouraud claimed that the bacillus isolated by him was the cause of **oily seborrhea** and also of **alopecia areata**, which he considered a localized seborrheic condition. He was the first to describe accurately the cultural properties of the organism, which he named "bacille de la séborrhée grasse." As according to Sabouraud's method the extruded plugs were always put down into the culture medium, he apparently unconsciously did the very thing required by the acne bacillus for its ready growth. It is an anaërobe, although it will grow feebly under partial aërobic conditions. Halli and Civatte (Ann. de Dermat., vol. viii, p. 184, 1907), in making anaërobic cultures from comedones, constantly found colonies of an anaërobic organism which corresponded very closely with the organism isolated by Sabouraud. Südmersen and Thompson (Jour. Path. and Bact., vol. xiv, No. 2, p. 224, 1909) insist upon the anaërobic requirements of the acne bacillus; using merely a 2 per cent. glucose agar and growing their cultures anaërobically, they are able to get very satisfactory isolation. Hartwell and Streeter (Boston Med. and Surg. Jour., vol. clxi, No. 25, p. 92, Dec. 16, 1909) again call attention to the fact that the *Bacillus acnes* is essentially an anaërobe. The bottle bacillus mentioned by Sabouraud and others is a large organism shaped something like a bottle, presenting an appearance very much like a yeast. It occurs in the more superficial parts of the comedone, and is found constantly in dry seborrheic conditions of the scalp or elsewhere, where its presence has been considered of great diagnostic value.

Gilchrist (Johns Hopkins Hosp. Rep., vol. ix, p. 409, 1900; Jour. Cut. Dis., vol. xxi, p. 107, 1903) was the first to obtain pure cultures of the acne bacilli directly from lesions of acne vulgaris or from comedones; he renamed the organism *Bacillus acnes*. Gilchrist found the bacillus present in all smears from 240 typical acne lesions from 36 patients; pure cultures of the *Bacillus acnes* were obtained from 62 lesions from 29 patients; 82 cultures were sterile, most of these because the proper medium was not used, and the cultures showed either a growth of *Bacillus acnes* mixed with staphylococci or the latter in pure culture. The bacillus was described as a short, thick organism in the smears and in cultures it became longer, thicker, and branched. Irregular staining was noticed in older cultures. It does not decolorize by Gram's method and is not encapsulated.

Interest was raised in the etiological significance of the acne bacillus by the work of Fleming (Lancet, vol. i, p. 1035, April 10, 1909). He had noted that very frequently in treating a case of acne with staphylococcus vaccine there was definite improvement for a time, and then the condition remained stationary in spite of any modification in the dose or character of the staphylococcus vaccine. He then took up the study of the relation between the acne bacillus and these resistant cases, with the result that he has finally proved the *B. acnes* to be the cause of acne. Fleming believes the *Bacillus acnes* is the cause not only of the comedone, but it may also be the cause of pustulation, while Whitfield (Lancet, vol. i, p. 1207, 1909) maintains that suppuration in acne is due to staphylococci. Fleming found that there was a very

close corelationship between the opsonic index and the clinical condition of the patient, but the clinical condition rendered the continuance of opsonic estimations unnecessary for guidance in treatment. One patient exhibited a marked negative phase with 10 million bacilli to whom had previously been administered a dose of 50 million. Each dose was followed by a very luxuriant crop of pustules, and from these pustules pure cultures of the acne bacillus were obtained. In most of his work Fleming used a stock vaccine; in some instances he used autogenous vaccine and in others autogenous and stock concomitantly. The stock vaccine was derived from a pustule on the face of a woman who had had severe pustular acne for many years. She had been receiving staphylococcic inoculations at intervals of ten days for about a year. The condition had improved somewhat at first, but for some months had remained almost stationary. She then had the same stock staphylococcus vaccine combined with 20 million of her own acne-bacillus vaccine. This was followed by the appearance of fresh pustules and aggravation of existing ones. Such treatment was continued with the doses of acne bacilli varying from 5 to 10 million; in three months almost all traces of acne had disappeared. Fleming continues: "Another case was that of a girl about 26 years of age, with a very bad pustular acne on the face for several years. The face was covered with deep, indolent pustules; a film of pus showed no organisms; of cultures from 4 pustules 2 were sterile and 2 showed a scanty growth of staphylococcus.

"From July till the end of September last year she had doses of mixed-stock

staphylococcus and acne-bacillus vaccines in doses of 100 to 250 million of the former and from 5 to 20 million of the latter, with hardly any improvement. It is worthy of note that while a dose of 250 million staphylococci plus 10 million acne bacilli produced hardly any negative phase, the next dose of 250 million staphylococci plus 20 million bacilli was followed by a marked exacerbation of the pustulation, indicating the importance of the bacillus in the causation of these lesions. From the end of September till the beginning of January she had the same doses of staphylococcus with doses of from 5 to 10 million of an acne bacillus obtained in pure culture from her own pustules, and from the very first her condition improved till on January 7th of this year all suppuration had disappeared from the face with the exception of 1 very small, superficial pustule.

"Another case was that of a girl aged 20 years, who had had very bad facial acne for five years. Films of pus showed many acne bacilli and in some pustules staphylococci were also to be seen. From September 3d to December 3d, 1908, she was treated with stock vaccines of staphylococcus (200 million) and acne bacillus (5 to 8 million) without showing any definite improvement. From December 3d to January 22d, 1909, she has been having the same doses of the same staphylococcus with 8 million of an acne bacillus derived from her own lesions. The improvement was immediate and marked, and now there is practically no pustulation, merely some indurated nodules and many scars.

"These cases illustrate the fact that not all patients will show improvement when treated with a stock vaccine, and

this is exactly in accordance with what one finds with other organisms, such as streptococcus or *Bacillus coli*. They also furnish very strong evidence that the bacillus is largely responsible for the suppuration. The first case had been treated with staphylococcus for months, and it was only after acne-bacillus vaccine was administered that a rapid improvement in the pustulation was observed. The first and second of these cases show that when an excessive dose is given them a definite negative phase is induced, although the dose of staphylococcus is unaltered. The second and third cases show that although the stock vaccine of staphylococcus combined with the stock vaccines of acne bacillus was of little avail, yet the same doses of the same stock vaccine of staphylococcus with an autogenous acne-bacillus vaccine rapidly got rid of the suppuration.

"While these cases illustrate the fact that in some cases an autogenous vaccine of acne bacillus is necessary, yet experience has shown that in the vast majority of cases great improvement has been induced by the inoculation of a stock vaccine combined with staphylococcus if an examination of films has revealed that that organism is present. The dose used has varied from 4 to 10 million, and the intervals between inoculations from one to two weeks. The guide to treatment has been the appearance of fresh lesions either during the period of low resistance following the positive phase when too long an interval has been allowed to elapse, or in the next two or three days after an inoculation indicating that too large a dose has been administered. By watching these signs and working the dose up till it just fails to show any 'nega-

tive phase' clinically one obtains the maximum benefit from the vaccine. In this way a large number of cases of acne in all its stages have been greatly improved, and in a fair proportion the lesions have totally disappeared. On cessation of treatment in several instances, especially in some cases where attendance ceased before the condition had entirely disappeared, there was a recrudescence of the disease, which, however, rapidly gave way to subsequent treatment."

Lasseur (Ann. de Dermat. et de Syph., 5th series, No. 1, pp. 377-382, 1910) has treated 20 cases of **pustular acne** by the method of Wright. Patients were not submitted to any other treatment, local or general. In 9 of the pustular cases with comedones he has observed an effect manifestly favorable, although the effect of a vaccine composed of a mixture of acne bacilli and staphylococci has given much more favorable results. In 8 cases the effect has been almost *nil*.

Western (Brit. Jour. of Dermat., Jan., 1910) found that by rubbing cultures of the acne bacillus into the sterilized skin of susceptible individuals pustular folliculitis is produced from which the acne bacillus can be recultivated.

Walsh (Med. Press and Circ., vol. lxxxix, pp. 80-82, Jan. 26, 1910) states that the treatment of acne is satisfactory when begun early in the disease. The best results are said to be those in which the vaccine has been prepared from cultures derived from the patient himself, but as the plan is too costly for hospital work it is fortunate that the use of a *polyvalent vaccine answers well enough* in most cases. Where the chief feature is a **comedo**, acne-bacil-

lus vaccine alone is indicated. In other cases a mixed vaccine of 200 million staphylococci and 8 million acne bacilli is used. The dose is gradually increased to the maximum with intervals of about ten days. Walsh has found the treatment to yield durable results in some cases, while others recur afterward or show no appreciable improvement.

D. King Smith (Jour. Cut. Dis., vol. xxix, pp. 432-435, 1911) has treated about 150 cases of acne vulgaris. The patients have been divided into three classes: A, those with the acne bacillus alone; B, those infected with the acne bacillus and the *Staphylococcus albus*, and, C, those affected with the *Staphylococcus albus* in which practically no bacilli were present. Class A patients were treated with acne vaccine, the dose being 5 million, repeated twice a week. The results in a number of cases were good, but on the whole were disappointing. The final conclusion was that along with a general and local treatment the vaccine is useful. The results were better in Class B with a mixed vaccine, while those in Class C gave excellent results.

From the standpoint of the application of proper accessory methods, size of dose, and intervals between injections, Engman (Interstate Med. Jour., vol. xvii, pp. 943-959, 1910) has appreciated and applied the principles of vaccine therapy more thoroughly and systematically than anybody else who has contributed to the literature on the treatment of acne by bacterial vaccines. He says: "From our experiments, the following technique has been developed: The initial dose is never over 3 million, and it is not given until two or three days after

cultures have been taken, as manipulation of the lesions throws more immunizing bodies on the system, which, together with the vaccines, is too much and may defeat the end. I have often wondered at the prompt appearance of many new lesions after a vigorous massage of an acne skin or after opening many lesions. I have seen several outbreaks of acne follow treatment by a masseur, which I formerly thought due to infection by him, but now believe to be dissemination through local lowered immunity. After a dose of 3 to 5 million, 1 or 2 new lesions will appear within forty-eight hours, generally the next day. If more than 3 appear during the negative phase, the dose is too large. On the third day, seventy-two hours after injection, the comedones are expressed and all lesions opened. The manipulation at this time brings the immunizing blood to the part, since it is at the height of the 'tidal wave of immunity.' The large cystic lesions are opened by a thin cataract knife and the pus is squeezed out; the walls of the lesion are in this way rubbed together, and by irritating them fresh immunizing lymph is brought into the cavity. Formerly, these large cystic lesions took a long time to heal; often it was necessary to wipe them out with carbolic acid and alcohol before they would cease discharging. This method dried them up within a few days. The patient is also instructed to apply hot towels to the face twice daily for five minutes so as to cause local hyperemia. On the fifth to the seventh day new lesions will appear, which signify another stage of depression and are the indication for a second dose of vaccine.

Another dose of 3 to 5 million is given; in this way a cure is completed. Small doses, sufficient to cause a short negative phase, seem with us to be the best method. After several doses new lesions cease to appear.

"If after a few doses new lesions appear after the third day, a larger dose of 7 to 10 million should be given, but this is rarely necessary. Small doses at from five- to seven-day intervals, with methods employed to produce local hyperemia, thereby bringing the immunizing blood to the part, are sufficient to secure immunity in the majority of instances. By this technique all lesions, even the deep, indurated ones, undergo comparatively rapid involution. Cases of acne of years' standing, which have resisted the most approved therapy of some of the most eminent men, have responded kindly to this form of treatment.

"A remarkable and gratifying thing is that the thick, muddy, yellowish, oily appearance of the skin disappears. The texture of the skin also improves, and a pinkish tint supervenes. The oily seborrhea of the scalp improves. It seems as if Sabouraud's dicta are true. We know the oily, yellowish-tinted skin precedes the acne lesions for a considerable time.

"It has not been found necessary, in any of our cases of acne vulgaris, to use staphylococcus vaccines; at least, not since we have employed the method above outlined. The acne bacillus seems to be the offending agent alone, and, although accompanied by the staphylococcus in nearly every lesion, the lesion is not a result of symbiosis, the coccus

being, no doubt, only a secondary factor of no therapeutic importance.

"In *acne varioliformis* the rôle is changed, turned about completely, the staphylococcus being the main factor, and the acne bacillus, which is frequently associated with it, a secondary, unimportant element. Acne vulgaris is essentially a disease of puberty, while acne varioliformis usually occurs after 30. Our experience is not sufficient to state whether the immunity after the use of these suspensions is permanent or not.

"The above is part of my report submitted to the American Dermatological Association last May. Since then I have studied 90 additional cases, making a total of 208 in all, and must say that I have no reason to change my opinion as to the value of acne-bacillus suspensions in the treatment of acne vulgaris.

"One must not forget, however, in carrying out the technique of this method, that one is not using a specific serum, where a definite dose is known, nor crude salves or lotions, but is dealing with the subtle and little-known principles of immunity; and that failure in an individual case, or cases, should not necessarily mean the condemnation of the method.

"I have seen some of the worst cases of acne disappear in a most wonderful and rapid manner after the injection of a few million of dead bacilli without any local treatment or change in diet whatsoever. Again, I have seen very matured cases of acne seem stubborn and almost unimproved under the same treatment. Yet in every case treated by this method, which I have seen, a cure has ensued when the case has remained

long enough to allow a profitable study of the individual dose and interval of dose. The method depends necessarily upon the size of the dose and the interval of the dose."

Varney and Clark (Jour. Cut. Dis., Feb., 1912) have called attention to a micrococcus with unusual characteristics which they found in a resistant dermatosis resembling acne vulgaris. These cocci more closely resemble diplococci than staphylococci. They take the ordinary stains more readily and appear more evenly distributed in the smear, being arranged in short chains, tetrads, and small clumps. Culturally the organism resembles the *Staphylococcus pyogenes albus* very closely; the growth is slightly whiter and somewhat less luxuriant on agar. It produces no visible change in plain milk, but causes litmus milk to turn alkaline slowly. It does not ferment any of the sugars nor produce indol. The 5 cases from which this micrococcus was isolated were uniformly of unusually long duration, all existing longer than eight years and 1 twenty-four years. All were beyond the age of the acne-vulgaris patient. Four of the patients had received inoculations of combined staphylococcus and acne-bacillus suspension, with only slight transitory improvement. The 5 cases recovered rapidly when treatment was started with vaccines containing the organism described by Varney and Clark.

Cooke and Dold (Practitioner, vol. lxxxiv, pp. 526-531) have studied *seborrheic conditions* of the scalp with the idea of determining whether or not the acne bacillus is the cause of such conditions. They treated 8 cases

by injections of acne bacilli; the treatment had no apparent effect on the disease—at least, it had no permanent effect. In 2 cases there was an alteration of the condition observed throughout the whole treatment, while in 3 others there seemed to be improvement in the first month which was followed by a return of the condition.

According to Sibley (Clinical Jour., Apr. 29, 1914), severe cases of acne often do better under vaccine treatment than comparatively mild ones; the most resistant to this treatment are usually those with abundant seborrhea, many comedones, and scanty foci of suppuration. Vaccine treatment must be continued for 6 months at least, and long after all spots have ceased to appear, when diminishing doses at longer intervals will often prevent relapses and complete a cure.

Rebellious cases of acne were scarcely influenced by the vaccine in cases treated by Spillman and Zuber (Progrès méd., Apr. 11, 1914), except that pustular lesions became much smaller, less numerous, and more evanescent after the treatment.

In Cornell University, H. H. Fox (Jour. Amer. Med. Assoc., June 24, 1916) found that entering students showed 30.2 per cent. of the freshman class suffered from acne vulgaris; general in 17.8 per cent., and limited to the face in 12.2 per cent. Their treatment showed the superiority of well-known therapeutic measures over vaccine therapy. Indeed, T. J. Horder has well said: "The failures of vaccine therapy are probably more numerous than its successes."

Strickler and Schamberg (Trans. Amer. Assoc. of Immunol.; Med. Rec., July 13, 1918) found in the treatment

of acne by vaccines that there was a complement fixation in 63 per cent. of cases from an antigen prepared from colon bacillus isolated from the intestinal tract of the patient. The fixation was higher when the antigen was from the patient. It was resolved to treat fifty cases with no other means than by vaccines prepared from an autogenous colon bacillus. These cases were controlled by cases treated by other methods,—vaccines from other germs, therapeutic and hygienic measures. The *B. coli* vaccines were found to possess better curative effects than any other mode of treatment.

J. F. Schamberg emphasized that vaccines prepared from *B. acne* and from staphylococci had been used for many years, and in some cases had given brilliant results, in others they had failed to respond. The present experiments were tested out in a hospital clinic with a large number of patients. Sixty-three per cent. gave positive complement fixation to the strains of *B. coli* used for the vaccines. A large percentage of patients responded to a remarkable degree. It was likely that at puberty, when there was great developmental activity, that there was liability to infection from the intestinal tract. The activity of the intestinal organisms would then produce noxious effects. The complement fixation tests would incriminate especially the colon bacillus.

Dr. Strickler now welcomed an active case as he felt that a good deal could be done for the patient. Formerly he had rather dreaded to see such a patient come, as the results of treatment were so often disappointing.

PERTUSSIS.

Bordet and Gengou have shown that whooping-cough is due to a small

organism resembling the influenza bacillus. It is more easily isolated during the earlier than the later stages of the disease. The *B. pertussis* is a constant factor in the disease and the symptoms are probably due to toxins and endotoxins liberated by it. Like other inflammatory conditions of the upper respiratory passages, it is more than probable that secondary infections play a very prominent part after the condition has established itself. It is possible that the generally unsuccessful results attending the experiments with Bordet's therapeutic sera and with bacterial vaccines are due to the lack of specific effect of such agents upon the *accessory bacteria*. Although Bordet and Gengou have done a great deal of work along this line since the discovery of the bacillus in 1906, they have persistently refused to commit themselves in favor of any preparation to be used as a serum or a vaccine. S. Becker and v. Menshikoff (Cent. f. Bakt., i, orig., p. 218, Dec. 9, 1911) treated some patients in the third and fourth weeks of the disease and others in the fifth and sixth weeks, their ages varying from 11 months to 9 years. The injections were made weekly, increasing the dosage. The first dose was 5 million; the second dose, 10 million; the third dose, 20 million; then 50, 100, and 200 million.

More favorable results have been reported by Graham (Amer. Jour. of Dis. of Child., vol. iii, pp. 41-49, Jan., 1912): He injects 40 million bacteria in the intrascapular region every two days. The number of injections given varied from 6 to 8. No case has been recorded in which less than 6 doses were administered, and none of the patients received more than 8 injections of 40 million each, except No. 22, who

had 9 injections. In not a single instance were evidences of local inflammation noticed at the site of the injections, and, while most of the injections were given in the loose tissues of the scapular region, some children received injections into the arms.

Paul Luttinger (Jour. Amer. Med. Assoc., May 19, 1917) summarizes the results of 180 physicians to whom the Bureau of Laboratories of New York, have supplied pertussis vaccine over a given period of time, and also the results obtained in the City whooping cough clinic. He says that the results obtained at the whooping cough clinic warrant the routine administration of pertussis vaccine for both curative and prophylactic purposes. The best time to institute the vaccine treatment, except as a prophylactic, is the first and second week of the paroxysmal stage. When the proper vaccine is given and the method of the department is employed, the disease is materially reduced in duration and severity.

In 155 cases of pertussis that had been under way from 5 to 45 days in all but 3, a large proportion being less than a year old, Caronia (Pediatrics, June, 1917) reports 61.28 per cent. cured, 32.25 per cent. improved and only 6.45 per cent. not influenced from systematic vaccine treatment. Some required only from 3 to 5 injections, others 10. In the cases with negative results the Bordet-Gengou bacillus was generally not found in the sputum.

H. L. K. Shaw (N. Y. State Jour. of Med., Jan., 1918) used vaccines in 112 cases of whooping cough as the only treatment. In 36 per cent. of the cases in which the vaccines were given after the whoop developed, the course of the disease was shortened, but with no effect on the number and severity of

the paroxysms; in 52 per cent. there were fewer paroxysms and of lessened severity, especially at night; in 12 per cent. of cases there was no improvement.

Rosenthal (Medical Council, June, 1918) states that the use of vaccine in the treatment of pertussis has proven to be entirely satisfactory in from 80 per cent. to 85 per cent. of his cases, and that the earlier in the course of the disease the treatment was begun, the more positive the result. He urges large doses, not less than 1 billion as the initial dose, increasing 1 billion every second day, unless a reaction is produced, until 3 or 4 billion are given, continuing this dose every second day until well. Usually from 5 to 8 doses will be found necessary. He found the best vaccine to be the mixed stock vaccine containing Bordet-Gengou bacilli, pneumococci, micrococci catarrhalis and streptococci.

According to Huenekens (Amer. Jour. Dis. of Children, July, 1918), pertussis vaccine from 2 to 3 months old, employed in very large doses, 1 billion and over, immunizes in only 12.5 per cent. of cases. Two to 4 weeks old vaccine confers immunity in from 25 to 75 per cent. of cases. Freshly prepared vaccine, employed in the same dosage, shows evidence of antibody formation in 94 per cent. of cases. When used in still larger doses, 1, 1½ and 2 billion, 100 per cent. positive reactions are obtained. The antibodies are demonstrable within one week after the last injection. Pertussis vaccine less than 1 week old should be employed only when freshly prepared and without preservative. The most effective dosage is 1 billion, 1½ billion and 2 billion, given on alternate days, for three doses. It is most effective as a

prophylactic, but should be of great value in the early catarrhal stage of pertussis. In doubtful cases of pertussis the vaccine should be administered before an exact diagnosis can be made, especially during an epidemic.

ASIATIC CHOLERA.

The idea of vaccine prophylaxis of Asiatic cholera has been combated almost from its inception, but it has little by little gained favor until at present the number of its partisans has been considerably augmented. Ferran (C.-r. de l'Acad. des Sci., vol. c, p. 569, 1885) showed that animals having once survived the inoculation of a non-fatal dose of cholera vibrios could later easily withstand a dose fatal for normal guinea-pigs. The idea of Ferran of using living germs was severely attacked and criticised, and seemed definitely condemned when Gamaleia (C.-r. de l'Acad. des Sci., vol. cvii, p. 432, 1888) reopened the question by suggesting vibrios killed by heat. Tanancheff (Ann. de l'Institut. Past., p. 713, 1892) suggested phenol instead of heat for killing the bacteria. Many attempts have been made to make practical a method of vaccination by the intestinal route. Klemperer, Sawtschenko and Zabolotny, and others tried such methods upon themselves. Metchnikoff (Ann. de l'Institut. Past., p. 541, 1894) believes that subcutaneous inoculation of antigenic substances cannot immunize a person to an infection like cholera, which is almost purely intestinal. He experimented with intestinal immunization, but was forced to conclude that "the ingestion of cholera cultures does not certainly protect against the pathogenic effect of Koch's vibrio."

The method of Haffkine involves the use of two vaccines, a weaker and a

stronger. The weak vaccine is obtained by growing the bacteria on agar at a temperature of 39° C. in a current of air. The stronger vaccine is prepared by passing the vibrios through a series of guinea-pigs until a virus is obtained which is invariably fatal to these animals within eight hours. Injections are given hypodermically in the flank, and an interval of five days should separate the two inoculations. The degree of protection afforded by the vaccination is said to be proportional to the severity of the symptoms caused by it. Before employing the vaccines generally Haffkine tried them on himself and others. No ill effects were produced. Reporting his experiences in Calcutta and Lucknow, Haffkine (Brit. Med. Jour., i, 219, 1895), gives the following figures:—

Population	Cases.		Deaths.	
	Total.	Perct.	Total.	Perct.
Non-inoculated	1735	174 10.63	113 6.51	
Inoculated	500	21 4.20	19 3.80	

C. Dopter (Paris médical, Jan. 2, 1915) calls attention to the efficiency of anticholera vaccination in the Balkan wars. Whereas the incidence of cholera among 14,332 unvaccinated officers and enlisted men was 5.75 per cent., that among 21,216 men vaccinated once was but 3.12, and among 72,652 men vaccinated twice, 0.43, according to Arnaud. In the civil population of Greece, Cardamatis reported percentages of 2.12, 0.26, and 0.01, respectively. The vaccine used in these cases had been prepared at the Pasteur Institute in Paris and consisted of cultures on agar heated to 60° C. for 1 hour. The writer considers 3 injections at 5-day intervals essential if immunity is to be acquired. Doses of 1, 1.5, and 2 c.c. respectively, should be administered.

In the Hungarian army, Fejes (*Deut. med. Woch.*, Apr. 6, 1916) found cholera inoculations much less efficacious than the typhoid. Aside from its undetermined protective power, it did not mitigate the course of the disease.

Konrádi (*Zentralbl. Kakt.*, 1916, Part I, p. 339) states that after vaccination the blood will show agglutination for about a year. The protection conferred by vaccination depends upon the number of inoculations, the dosage, and upon the mode of living. An annual dose of 0.5 c.c. is sufficient. The vaccination is free from danger even to children. The author employs Kolle's method of preparation of cholera vaccine. The bacterial emulsion is heated for one hour at 55° C. One-half per cent. phenol is added. One c.c. of the emulsion contains 2 mg. of culture. The first dose is 0.5 c.c. An additional 1 c.c. is injected after one week. The symptoms are slight and usually disappear within two days.

H. E. Keisten (*Münch. med. Woch.*, May 21, 1918) has noted that the effect of the vaccination does not last for more than 5 months, so that it should be repeated before the lapse of that time. At the beginning of an epidemic subjects formerly vaccinated may be again vaccinated even when they already show the early symptoms of cholera. There need be no fear of setting up a negative phase. Quite on the contrary, revaccination has seemed to give very happy therapeutic results.

BUBONIC PLAGUE.

Bubonic plague is historically one of the most interesting of the infectious diseases. Epidemics have occurred in all parts of the world, carrying off millions of people. The causative organism was discovered by Yersin (*Ann.*

de l'Institut. Past., vol. viii, p. 662, 1894). Roux, with Calmette and Borrel, made the first trials to vaccinate animals with heated cultures. Inspired by the work at the Pasteur Institute, Haffkine prepared his "plague prophylactic" and obtained permission from the British government to use it in India. His method is as follows: Plague bacilli are grown in broth culture for about six weeks. A few drops of oil or clarified butter are put upon the surface of the fluid. The bacteria attach themselves to these and hang down in the broth in the form of stalactites. The flask is shaken every few days to cause the bacteria to fall to the bottom of the fluid and more stalactites develop. It is believed that this method greatly increases the amount of growth. The bacilli are then killed by exposing the culture to heat (65° to 70° C.) for one hour. Haffkine at first added no preservative, but later used a small percentage (0.5 per cent.) of phenol. At present the method in use at the Pasteur Institute is more like that employed for the preparation of other bacterial vaccines. The cultures are grown on agar for about twenty-four hours and suspended in saline solution. They are killed by heat, and 0.5 per cent. phenol is added to them. The number of bacteria contained in the vaccine is not standardized by counting; an effort is made to have the suspensions uniformly turbid. The dose of Haffkine's original vaccine was 3 c.c. for an adult man, 2 to 2½ c.c. for women, and smaller doses for children. It is given by subcutaneous injection. Local and constitutional symptoms of moderate severity may follow. There is redness and swelling at the point of inoculation and sometimes a rise of

temperature of 2° or 3°. These symptoms subside within twenty-four to forty-eight hours, and do not, as a rule, necessitate the abandonment of ordinary occupation. Haffkine believes that protection against plague is produced rapidly—within twenty-four hours. Wright believes it is likely that there is a period of increased susceptibility corresponding to the negative phase; Calmette has agreed to this. Bannermann denies that such is the case, and considers that the injection does not aggravate an attack even if made during the incubation period. This latter opinion agrees with the ideas of Russell, that the negative phase is not of great importance and does not increase the individual's susceptibility to the disease.

Haffkine (*Lancet*, vol. i, p. 1697, 1899) gives the results obtained with inoculations in the village of Undhara. Among 64 uninoculated persons there were 27 cases of plague and 26 of these proved fatal; while among 71 inoculated persons, members of the same families as the former and living under exactly the same conditions, there were 8 cases, 3 of which were fatal. The deaths among the uninoculated thus exceeded the inoculated by 89.65 per cent.

In the prison of Byculia, at Bombay, where an epidemic of plague had broken out, 147 prisoners were inoculated, while 172 uninoculated prisoners were allowed to remain as controls. As a result there were 12 cases and 6 deaths among the uninoculated, while among the vaccinated there were 2 cases, both of which recovered. Haffkine (*Bull. de l'Inst. Past.*, vol. iv, p. 85) sums up the results so far obtained with the following figures:—

Inoculated ... 186,797—	3,399, or 1.8 per cent.,
	attacked with plague;
	814, or 0.4 per cent.,
	died.
Uninoculated 639,630—	49,433, or 7.7 per cent.,
	attacked with plague;
	29,733, or 4.7 per cent.,
	died.

The report of the Indian Plague Commission with regard to the value of Haffkine's prophylactic was as follows:—

1. Inoculation sensibly diminishes the incidence of attacks of plague. It is, however, not an absolute protection against the disease.

2. The death rate is markedly diminished by its means, not only the incidence of the disease but also the fatality (case mortality) being reduced.

3. The protection is not conferred, on those inoculated, for the first few days after the injection.

4. The duration of the immunity is uncertain, but it seems to last for a number of weeks, if not for months.

Many different forms of vaccine have been recommended besides the Haffkine prophylactic; for instance, attenuated living cultures have been employed in the Philippines by Strong (*Amer. Med.*, p. 272, Aug. 15, 1903). Shiga has used a serovaccine in Japan. Sensitized bacteria as recommended by Besredka have been used with apparent success in Mexico and Peru.

The uniform success attending the use of typhoid vaccine as prepared and standardized at present will doubtless suggest to many the advisability of using the same system for prophylaxis against bubonic plague; in other words, there would seem no good reason why the injections should not be spaced seven to ten days apart and the doses adjusted to contain 500 and 1000 million bacilli for the first, second, and third doses, respectively.

DISEASES OF THE EYE.

The treatment of eye diseases by serums and vaccines, which has received much attention in recent years, differs somewhat from similar treatment of disease in any other part of the body on account of the anatomical peculiarities of the blood- and lymph-supply of this organ.

The cornea and vitreous normally have no blood-vessels, and are only feebly nourished by lymph; the lymph-circulation is not free, especially in the intrinsic parts of the eyeball; this is exemplified by the rarity with which malignant growths of the interior of the eyeball give rise to secondary deposits in glands before the growth, by direct extension, has spread outside the sclerotic coat. Again, in those parts of the eye where there is a supply of blood-vessels the amount of blood in these vessels is constantly varying, owing to the unceasing movements of the eye as a whole, and of its various parts—the iris, ciliary body, etc. These movements are of importance when the eye is infected, as they cause the liberation of bacterial substances, toxins, etc., into the blood-stream. In the treatment of eye infections, the use of autoinoculation methods are essentially unsatisfactory, and in using vaccines it is necessary as far as possible to prevent autoinoculation by keeping the diseased part at rest. Should autoinoculation occur while vaccine inoculation is being carried out, substances of unknown amount may be set free in the blood-stream at unfavorable times, interfering with the regulation of the dosage of vaccine.

Since the area infected is so small

there is less danger of a general toxic reaction from an overdose of vaccine, and on account of the limited blood- and lymph- supply relatively smaller amounts of bacteriotropic-carrying fluids are brought to the infected area. Relatively larger doses of vaccine may therefore be administered in treating diseases of the eye for the purpose of obtaining an ultimately greater concentration of antibodies in the blood and lymph.

Bryan ("Serum and Vaccine Therapy in Connection with Diseases of the Eye," B. M. J., pp. 542, 662, 722, Mar., 1912) says it is possible without the opsonic index to regulate the amount of vaccine to be administered, since it is possible by direct inspection to observe and follow the course of the clinical manifestations. In diseases of the iris, cornea, and sclerotic, vascular injection of the conjunctiva decreases after an efficient dose of the vaccine, though if a negative phase is produced the injection may be temporarily increased.

Tuberculous Infections.—The treatment of tuberculous conditions of the eye has been about as successful as the treatment of localized tuberculous infections in other parts of the body. The lesion may be secondary to pulmonary tuberculosis, in which case the infecting organisms are probably of the human type; it may also be secondary to tuberculous cervical or mesenteric lymph-nodes. In the latter the bacilli may be of the bovine type. This differentiation is considered of importance in treatment by Spengler, Raw, and others, who believe their results are better when they use the heterologous tuberculin. Bacillen emulsion seems to be the

tuberculin preferred by the majority of English writers, although other preparations have given equally good results in the hands of others. The system of administration is the same as for tuberculous lesions elsewhere. The initial doses should be small ($\frac{1}{80000}$ to $\frac{1}{10000}$ mg. according to Wright) and increased gradually over a long period of time. The tuberculin should never cause a temperature reaction.

Bryan (*loc. cit.*) has treated successfully various extrinsic tuberculous conditions of the eye, namely: tuberculous conjunctivitis, interstitial keratitis, scleritis, sclerokeratitis, and phlyctenular ophthalmia. Among the internal affections of the eye, iritis, keratoiritis, iridochoroiditis, and choroiditis have terminated favorably when submitted to tuberculin treatment. Hancock and Mayon, von Hippel, Collins, Lawford, Dubey, Fromagat, Bruckner, and Hay all report favorably.

Carmalt Jones ("Introduction to Therapeutic Inoculation," London, MacMillan, p. 141, 1911) has treated 9 cases of **phlyctenular keratitis**. Of these, 3 were mixed infections; the others were tuberculous only; 5 were much improved, 3 improved, and 1, in which there were many different contaminating organisms, was unchanged.

Verheyden (Brit. Jour. Ophthal., 223, April, 1918) urges the more frequent use of tuberculin in **strumous eye affections** involving the conjunctiva, cornea, iris, ciliary body, sclera, choroid and tuberculous paralysis of the third nerve. A number of cases are detailed in which this treatment was highly satisfactory. Concomitant treatment consisting of 4 per cent. solu-

tion of dionin and subconjunctival injections of saline solution are useful adjuvants. He concludes that many eyes will be saved by tuberculin which would formerly have been lost or greatly damaged.

Gardini (Cronica Medica, Oct., 1918) emphasizes the necessity for small doses of tuberculin, avoidance of a febrile reaction, and long continuance of the tuberculin to ward off a relapse. There is no use in trying the tuberculin for ocular tuberculosis if there are already pulmonary lesions installed. Focal, local and general reactions show that we are on the right path, but warn to slow up some. The local reaction is of no moment except as an index of the patient's susceptibility. A focal reaction always occurred in the eye affected. He began with 1:10,000 mg. and very slowly and tentatively increased the dose to 1 mg. as the maximum, with 4 or 5 days' intervals. Three cases are described; the patients were 2 girls of 13 and a young woman. The tuberculous keratitis in the latter was of 3 years' standing and peculiarly tenacious. No benefit was apparent under the tuberculin treatment. The case teaches the lesson not to delay tuberculin treatment too long. One of the girls had had **keratitis** for 2 months and it improved to a clinical cure under the tuberculin treatment. In the other girl **iritis**, with a solitary tubercle and posterior synechia, completely and permanently retrogressed under the 3 months' course of tuberculin treatment.

External Infections.—*The Lachrymal Sac.*—Acute infections, especially those caused by the streptococcus, do not yield readily to vaccine therapy; but chronic infections, particularly

those pneumococci in type, yield readily, as a rule. **Chronic staphylococcal infections** also give good results, when treated by stock preparations. R. W. Allen (Practitioner, p. 737, 1908) has had success in treating with vaccines cases of **dacryocystitis** due to the streptococcus.

Disease of the Eyelids.—The *Staphylococcus aureus* is the cause of many varieties of chronic and recurrent disease of the lids. **Blepharitis** is usually due to errors of refraction, but when this is corrected staphylococcal vaccine is often an important adjuvant. **Chalazions** and **hordeola** which show marked tendency to recurrence have been cured by a three months' course of treatment by staphylococcus vaccine. Mayon (Ophthalmoscope, 1908) has treated 4 cases of acute **styes** associated with phlyctenules and corneal ulcers, in 1 of which a complete cure was obtained; in the other 3 there was a temporary relief, followed by recurrence. He also quotes cases of styes and recurrent **tarsal cysts** cured by one inoculation.

Conjunctivitis.—Many acute cases of ordinary conjunctivitis clear up rapidly by the use of antiseptics. Allen, however, recommends vaccine therapy in treating the condition when caused by the pneumococcus, streptococcus, coli, or pyocyaneus. **Gonococcal conjunctivitis** is of grave prognosis, and here vaccine is of great value. Bryan (*loc. cit.*) has treated 3 cases of gonococcal **ophthalmia** in newborn infants, and the disease was cured in each instance without infection of the cornea. Rubbrecht (Bull. de la Société Belge d'Ophthal., 27, p. 32, 1909) reports a case of systemic gonorrhea with

conjunctivitis and **keratitis** in which three doses of gonococcus vaccine (5, 7½, and 10 million) were given with excellent results. Ohlmacher (Jour. Amer. Med. Assoc., 48, 571, 1907) has reported the treatment of 3 cases of gonorrheal conjunctivitis, 2 of which were cured and 1 improved, while Miller (Glasgow Med. Jour., p. 356, 1908) has successfully treated 2 cases. Eyre and Stewart (Lancet, 11, p. 76, 1909) treated 1 case by this method, but without success. By examining the reports of various other writers we see that in acute gonococcal conjunctivitis, if the treatment be commenced before the internal parts of the eye are affected, good results may be obtained. But it is necessary to use very small doses, repeated at short intervals.

In a series of cases of ocular tuberculous manifestations excellent results were obtained by R. B. Metz (Cleveland Med. Jour., Sept., 1916) from the use of tuberculin in graded doses. It caused apparent cure or marked improvement in 5 cases, including 2 of **phlyctenular conjunctivitis**.

Chronic Conjunctivitis.—**Parinaud's conjunctivitis**, according to Sinclair and Sherman ("Trans. Ophthal. Soc. U. K.," vol. xxvii, p. 40) is probably due to *Staphylococcus albus*. No very favorable results with vaccine treatment are on record. Cases due to the diplobacillus of Morax, and others due to the Friedländer bacillus, have been benefited by vaccine treatment.

Phlyctenular Ophthalmia.—Mackey ("Trans. Ophthal. Soc. U. K.," vol. xxviii, p. 201) reports favorable results from the use of staphylococcal vaccine in a case of **phlyctenular keratitis** and **pustular episcleritis** of long-standing and many recurrences.

Gradle (Ophthalmic Record, p. 293, 1909) has reported 9 cases of phlyctenular infection due to the staphylococcus. The results of treatment with staphylococcus vaccine were satisfactory in all.

Ulcerations of the Cornea.—According to Bryan (*loc. cit.*) infections of the cornea are most commonly due to:

1. Staphylococcus. Vaccine treatment is favorable.

2. Pneumococcus.

(a) **Hypopyon ulcer.** Vaccine treatment gives a fair measure of success.

(b) **Ulcus serpens.** Vaccine treatment is usually followed by good results.

(c) **Hypopyon keratitis.** Usually the primary cause is tuberculosis; here tuberculin is indicated.

(d) **Keratomalacia** (a form of gangrene affecting the cornea in children enfeebled by wasting disease). Vaccine treatment is unfavorable.

3. Streptococcus infections are usually very virulent.

(a) **Hypopyon ulcer.**

(b) **Pseudomembranous ophthalmia** in children. Serums are probably preferable.

Allen (Practitioner, 80, 737, 1908) has treated 2 cases of pneumococcal corneal ulcer with perfect results; from another patient he isolated a small unidentified micrococcus, an autogenous vaccine was given, and this resulted in healing of the lesion. Eyre and Stewart (Lancet, ii, p. 76, 1909) were able to benefit 1 patient suffering with gonorrheal iritis by treatment with an appropriate vaccine, while 3 others were cured. Miller (Glasgow Med. Jour., p. 62, 1910) and Shumway (Ann. Ophthal.,

19, p. 233, 1910) have each treated successfully 1 case of gonorrheal iritis. Allen (*loc. cit.*) found the pneumococcus to be the infecting organism in 3 cases of **hypopyon**. Treatment with autogenous vaccine cured 2 cases and improved the other one.

In *postoperative infections of the eye* excellent results have been obtained with vaccines.

In *internal infections of the eye* due to pyogenic organisms, valuable results have been reported when a correct diagnosis was possible. Often when the condition is secondary to skin abscesses, puerperal infections, pleuropneumonia, etc., the causative organism is the staphylococcus or streptococcus. Another variety of metastatic infection may be due to pyorrhœa alveolaris, where the staphylococcus or the pneumococcus is the infecting agent. In all these cases, vaccines can be obtained from the primary lesions. When, however, there is no obvious lesion elsewhere the difficulty of obtaining cultures arises. In *iridocyclitis* cultures have been made from the aqueous humor after paracentesis by Mayon (Ophthalmoscope, 1908). He isolated staphylococci. Weeks ("Trans. Amer. Ophthal. Soc.," vol. xii, part ii, p. 598, 1910) treated a case of **gonococcal iritis** successfully with a stock vaccine, and mentions 2 similar cases treated by Oliver, and 1 of severe **gonococcal uveitis** treated by Posey, all of which improved. Other workers have isolated the streptococcus.

• ORIENTAL SORE.

The chronic and obstinate nature of Oriental sore in general and of the Cambay ulcer in particular has led to many methods of treatment. Such

drastic measures as curetting the lesions with a sharp spoon and salting the surface so freshened with powdered potassium permanganate are recommended. Other methods consist in the application of non-irritating antiseptic oils and ointment. Salol dissolved in olive oil, 1 dram to the ounce, has also been advocated. The oil penetrates the tissues more easily and therefore is more efficacious. Some have recommended arsenobenzol injections. This is a rather severe treatment for a benign, mild malady. A period of two or three months is always necessary for the healing process when any of the above-mentioned remedies are used. As the Oriental sore is a cutaneous inflammation of a low type, it is possible that the infecting parasite does not come into contact with antibodies in sufficient quantity or of efficient quality in the blood-serum supplying the part.

With the object of hastening the process of healing and of stimulating the mechanism of immunity production, Row (Brit. Med. Jour., p. 540, March 9, 1912) thought it might be desirable to attempt to make a curative vaccine much on the principle of Wright's staphylococcus vaccine for furunculosis. For this purpose massive cultures were made in the Nicolle-Novy-McNeal medium from the *Leishmania tropica* obtained from experimental lesions in the *Macacus sinicus*. When the cultures were well grown (on the seventh day) the fluid rich in flagellates was collected and suitably sterilized with glycerin. This "vaccine" was injected in tentative doses corresponding to 0.125 c.c. of original culture. When such a dose caused no constitutional or local reaction, a second injection of double the amount was made. Three cases thus

treated have healed rapidly. It may be possible to devise a similar autovaccine treatment for the kala-azar in Bombay.

MALTA FEVER.

Malta fever, or Mediterranean fever, was believed for years to exist almost exclusively on the Island of Malta. The known infected territory was later enlarged to include practically all the shores of the Mediterranean. In 1897 Wright and Smith (Brit. Med. Jour., April 10, 1897) confirmed the fact which Bruce and others had long surmised, that Malta fever is not confined to the Mediterranean basin, but is present in many parts of India. Musser and Sailer ("Proc. Path. Soc., Phila.," Feb. 1, 1899) reported the case of an army officer who apparently contracted the disease in Porto Rico. Strachan and Birt (Roy. Army Med. Corps, vol. xiii, p. 153, August, 1909) proved the disease to exist in goats in Asia Minor and South Africa. Recently Ferenbaugh (Jour. Amer. Med. Assoc., vol. lvii, No. 9, pp. 730-731, Aug. 26, 1911), and Gentry and Ferenbaugh (Jour. Amer. Med. Assoc., vol. lii, No. 14, p. 1127, Sept. 30, 1911) have called attention to the existence of Malta fever in Texas. Since many of the goats in Texas are direct descendants of animals imported from Asia Minor and Africa, it is not unlikely that the disease was brought over with them. Malta fever is particularly interesting since it has frequently been mistaken for typhoid fever. In the absence of facilities for making a correct diagnosis it has even been variously called "simple continued fever," "sweating fever" and "undulant fever." The main clinical features are fever more or less chronic in type, accompanied by constipation and copious perspiration. Convalescence is fre-

quently retarded by neuralgia, joint pains, and orchitis. The economic importance of the disease led the British Government to appoint a commission to study its nature and mode of transmission. This commission presented its report in 1907. Their conclusion was that goats are susceptible to the disease and are the carriers of the infection. They transmit the disease to man largely through their milk. Gentry and Ferenbaugh (*loc. cit.*) also believe that dust must be considered as a factor in its transmission in Texas; only the Mexicans as a rule drink goats' milk, while many cases of the disease are noted among visitors and other persons who do not drink goats' milk.

Malta fever was shown by Bruce, in 1887, to be caused by a small micro-organism which he named the *Micrococcus melitensis*. It may be isolated from the spleen of animals dead of the disease. The agglutinin reaction is of great value in differential diagnosis. The blood of infected persons will generally agglutinate the *Micrococcus melitensis* in dilutions of 1:80 and 1:100. Mohler and Eichorn (*Jour. Amer. Med. Assoc.*, vol. liii, 15, pp. 1107 and 1109, April 13, 1912) have recently called attention to the value of the complement deviation test for differential diagnosis. They believe it to be more reliable than the agglutination test.

Wright has successfully used a vaccine for the treatment of Malta fever. It was noteworthy in his case that during the negative phase the fever was high while during the positive phase the fever came down.

Reid ("Annual Report Sanit. Com. with the Government of India," p. 153, 1905) treated 9 cases with bacterial vaccines with good results.

His work was followed by Bassett Smith (*Jour. Hyg.*, p. 115, Jan., 1907), who treated 61 cases. He gave 224 injections in all. These cases comprised all grades of the disease from the severe undulant type to the intermittent. His vaccine was prepared by heating agar cultures of the micrococcus to 60° C. for half an hour. The initial dose used was generally about 50 million cocci; subsequent doses were rarely larger and the interval between injections was ten days. His conclusions were that vaccine treatment appears to produce beneficial results in a certain number of cases. In these cases the severity of the symptoms is diminished, the general condition is improved, and the duration of the disease curtailed. In the more severe types where high fever and evidence of severe intoxication are prominent the vaccine treatment seems to have a deleterious instead of a favorable reaction.

Chiriaco (*Pediatrics*, May, 1918) in relating 3 typical cases out of his extensive experience reiterates his statements as to the remarkable curative value of the Di Cristina-Caronia vaccine—in treatment of Malta fever. He declares that no time should be wasted on quinine, dieting and intestinal disinfectants. The vaccine should be given at once, as the patient grows worse under the other measures until irreparable damage results. He administers it by intramuscular injection. The results were always certain and extremely effectual, often actually remarkable from the rapid and complete disappearance of the infection.

DYSENTERY.

Infantile dysentery is one of the most fatal conditions affecting children under 1 year of age. The greatest number of

cases occurs during July, August, and the early part of September. Some years ago antidyenteric serum was used therapeutically in this condition, but without marked benefit. Recently Lucas and Amoss (Jour. Exp. Med., vol. xiii, pp. 486-494, 1911) have used vaccines *prophylactically*. "All the cases vaccinated were under 2 years of age and clinically showed no signs of dysentery or of any very acute gastrointestinal disorders. The vaccine was not administered to any child having a temperature above 38° C. In as many cases as possible specimens of the stools were obtained from the treated cases for bacteriological examination, and an equal number of control cases were followed bacteriologically and clinically. In this way it was hoped that some conclusion could be reached which would represent the value of this work carried out under the prevailing conditions.

"Out of the 95 patients vaccinated there were 2 deaths. In the 2 cases that ended fatally the original cultures were negative for the *B. dysenteriae*. Each patient received 2 vaccinations.

Hever and Lucksch (Wiener klin. Woch., Oct. 21, 1915) described an epidemic in a small town in which a mortality of 19.4 per cent. occurred in the 67 cases, all in about 8 months. All the sick were sent to a special hospital, and search was made for carriers in the infected houses. After this all the adults left were inoculated with a polyvalent vaccine, a total of 342 persons out of a population of 800. About 243 were inoculated twice. The reaction was always mild. The epidemic was promptly arrested.

Castellani (Brit. Med. Jour., Feb. 26, 1916) deems dysentery vaccination of great importance practically. Since

1912, he has prepared a mixed dysentery vaccine, and also a vaccine containing the mixed vaccine plus typhoid, paratyphoid A, paratyphoid B. Dysentery vaccine of this type should be prepared with a carbolic salt emulsion from agar cultures without heating, or peptone water cultures. Many strains of Shiga-Kruse bacillus should be inoculated in rabbits, and the least virulent, provided it be rich in antigen, should be kept permanently as a stock culture to prepare the vaccine. Broth cultures should never be used.

The not infrequent serious consequences resulting from the use of dysentery vaccines led Leonard Rogers (Brit. Med. Jour., Jan. 1, 1916) to try the effects of sensitized vaccines. The vaccines were stock ones of Shiga or Flexner strains sensitized with the Lister Institute antidyenteric serum. The single doses of these vaccines never exceeded 100 million. In most cases the results were very satisfactory.

Experiments on animals and a small number of tests on man by Olitsky (Jour. of Exper. Med., July, 1918) indicate that the single injection of an almond oil suspension of the Shiga and Flexner groups of dysentery bacilli suffices to afford protection as indicated by the appearance in the blood of definite specific antibodies for each group of the bacilli, and by the protection of animals from otherwise lethal doses of the living organisms or their toxic products.

In an experimental study of vaccination against dysentery by the oral route, Besredka (Presse méd., Aug. 15, 1918) found that when rabbits are caused to ingest killed cultures of the dysentery bacillus, the same clinical and pathological manifestations are produced as result from the living virus. According

to the weight of the animal and the dose of bacilli ingested, all forms of dysentery can be induced, from mild involvement with evanescent lesions to a grave form with bloody stools, terminating in death. A very light attack of dysentery, induced by ingestion of heated bacilli, suffices to render the animal refractory to infection by living and virulent bacilli. The immunity thus caused is such that the animal is enabled to withstand, by intravenous inoculation, a dose of the virus which kills the control in twenty-four hours. Besredka believes the procedure worthy of trial in man both for prophylactic and curative purposes.

In an experimental investigation of lipovaccines and a triple dysentery lipovaccine. Whitmore and Fennell (*Jour. Amer. Med. Assoc.*, Mar. 30, 1918) found that lipovaccines can be made on a large scale by growing the bacteria in Kolle flasks; taking off the growth with a vacuum scraper; freezing and drying in vacuo, and emulsifying in lanolin and oil by grinding in a ball mill, using glass bottles and steel balls. The oils can be sterilized by steam at 15 pounds for 15 minutes; by heating to 90° C. for 10 hours on a water bath, or by mixing with potassium iodide. Experiments are being conducted to ascertain whether or not this method of sterilization will affect the antigen power of the vaccine. Ultraviolet rays are also being tried in the sterilization of the oil; and tests are under way to determine whether the antigen substances are extracted from the bacteria in an oil-suspended vaccine by heating, as is the case in a vaccine suspended in saline. In administering the vaccine Whitmore and Fennell have found a needle, No. 21, B. and S. gauge,

with a cannula three-fourths of an inch long entirely satisfactory. Although the danger of fat embolism appears to be slight, they issue a definite warning that the injection should be made subcutaneously and care taken to avoid getting the vaccine into a vein. The writers found that they could give men a dose of 3000 million Shiga, 3200 million "T," and 2200 million Flexner type of the dysentery bacillus in oil without marked local or general reaction. They also ascertained that agglutinins, precipitins and bacteriolysins were produced in the blood of vaccinated animals and men, and that there was some evidence of complement fixation.

GLANDERS.

Considering the constant presence of glanders among horses, especially in large cities, and the extremely infectious and virulent nature of the organism, it is rather curious that no more instances of human infection have been recorded. It is highly probable that only a small percentage of human infections are ever actually recognized. The mortality rate is very high, and no previous method of treatment has appeared to have the slightest influence on the course of the disease. There are in the literature a number of cases of laboratory infection, nearly all of which have been fatal. The disease may assume an acute fulminant type in which death rapidly ensues. When it is more chronic in character the bacilli appear to remain quiescent in the tissues in various parts of the body for a considerable period. These foci may flare up and end in abscess or bring on an acutely fatal exacerbation.

Colebrook ("Proc. of the Royal Soc. of Med.," vol. iii, part i, p. 42, 1909-10) mentions an attempt to cure an infection with the glanders bacillus, which was unsuccessful.

Bristow and White (N. Y. State Jr. of Med., x, p. 236, 1910) have been more successful. In this case the initial dose was 10 million, and after fourteen injections at intervals of four to nine days a maximum of 300 million was reached. While the injections were followed by local and febrile reactions no untoward effects were noted, and the course toward recovery was consistently quite favorable.

Cramp (Jour. Amer. Med. Assoc., vol. lvi, No. 19, pp. 1379-1380, May 13, 1911) reports a case of **chronic glanders** in man treated with vaccine, apparently successfully. The patient has remained free from the disease for a period of eighteen months, is in good health, doing hard work daily, and has been under close observation. The vaccine was not accurately standardized, but was estimated to contain 14 to 20 million bacilli per cubic centimeter. The injections were given from four to seven days apart and a temperature reaction followed nearly every dose. After about three months' treatment all wounds healed and the patient's general health was excellent. He was given 5 more injections, however, at fourteen-day intervals. Cramp concludes that chronic glanders can easily be overlooked unless one is constantly on the lookout for the disease. Multiple abscesses, especially on the extremities, without definite cause should excite suspicion. This patient was apparently cured by vaccine injections.

OTITIS MEDIA.

Weston and Kolmer (Jour. Amer. Med. Assoc., vol. lvi, pp. 1088-1092, April 15, 1911) have made some valuable observations concerning the treatment of otitis media following scarlatina, their study being based on the treatment of 100 cases, extending over a period of nine months. They conclude that otitis media is a condition offering good hope for success by vaccine treatment, because the condition is local: the offending organisms can usually be easily secured: the infection soon becomes subacute and chronic and the results of treatment can be readily observed. The onset of the disease is frequently most insidious; a large number of children do not complain at all, and the first indication of trouble is the presence of discharge. On the other hand, many adults and older children suffer considerable pain. In a series of 406 cases the discharge first appeared on the following days of the illness, reckoning from the day of onset of the scarlet fever:—

Days of illness.	No. of cases.
1 to 5	27
5 to 10	97
10 to 20	155
20 to 35	81
35 to 49	35
49 to 84	11

"Patients suffering with severe throat symptoms, according to these authors, are most likely to develop suppurative otitis media by direct infection through the Eustachian tube. On the other hand, cases are apparently produced either by general blood infection or by the toxins of the disease.

"The first question is that concerning the best time for commencing vaccine treatment of cases of otitis media. Certain it is that a proportion of pa-

tients will recover in a reasonable length of time if left alone or given simple local treatment. It is equally certain that a proportion continue discharging for a long period of time, it may be for the remainder of life, the soft parts and finally the osseous tissue being involved. Experience has demonstrated that it is not wise to commence too early, and it is equally bad practice to wait too long, because long-standing cases are likely to be more refractory to treatment and the mechanism of hearing may be considerably damaged. During the acme and early decline of scarlet fever the patient may be having considerable fever; he may be toxic enough without the addition of vaccine or be suffering with acute nephritis and its accompanying toxemia; finally, the general condition may be so poor and the body defenses so busy combating the toxic condition that the administration of vaccine will evoke no favorable response, but produce injury by a prolonged negative phase, during which the organisms work increasing havoc. We commenced vaccine treatment in our cases according to the following table, reckoning from the first day of the onset of the otitis media as indicated by the presence of discharge:—

Time of discharge.	No. of cases.
Third to seventh day	6
Seventh to fourteenth day ...	33
Second to third week	21
Third to eighth week	28
Eighth to fourteenth week ...	10
Four years	1
Ten years	1

“According to our experience the best results were secured, considering all things, when cases were reported on the third day of the discharge. This enables one to watch the patient for a day or so; take a culture; consume five

or six days in isolating the organisms and preparing the vaccine. If at the end of this time the patient's general condition was fair and he was free of fever, nephritis and toxemia, a dose of vaccine was administered. If his condition was not favorable, the vaccine was put aside in a refrigerator. If at the end of ten days his condition warranted commencing the treatment, we did not use the first vaccine, for frequently a reculture will show a different organism or the presence of an additional offender. A reculture is made from the discharge and another vaccine prepared.

“The following table is a list of the organisms isolated from cultures of the 100 cases. If the otitis media was bilateral a culture was taken from each ear. If two organisms were found, each was isolated and a separate vaccine prepared. When administering two vaccines to the same patient, the aggregate dose was that equalling the dose of one organism. The bacteriology was comparatively simple and isolation readily accomplished:—

Staphylococcus aureus was found alone in 14 cases.

Staphylococcus albus was found alone in 2 cases.

Bacillus pseudodiphtheriæ was found alone in 35 cases.

Bacillus pyocyaneus was found alone in 20 cases.

Streptococcus pyogenes was found alone in 4 cases.

Staphylococcus aureus and *B. pseudodiphtheriæ* were found together in 9 cases.

Streptococcus pyogenes and *B. pseudodiphtheriæ* were found together in 4 cases.

Bacillus pyocyaneus and *B. pseudodiphtheriæ* were found together in 9 cases.

Streptococcus pyogenes and *B. pyocyaneus* were found together in 3 cases.

"If no improvement was noted after the third dose of vaccines, or if ten days elapsed before vaccine could be administered to a case after culture had been taken, a reculture was made and a new vaccine prepared. In many cases, an ear cultured three to four days after the onset of discharge will show the *Staphylococcus aureus*, while on reculture at a later date the *Bacillus pseudodiphtheriæ* will be found. Most of the long-standing cases yield *Bacillus pyocyaneus*, and repeated culturing can secure nothing else. The following table gives the list of organisms secured by recultures:—

Bacillus pyocyaneus was found alone in 20 cases.

Bacillus pseudodiphtheriæ was found alone in 6 cases.

Staphylococcus aureus was found alone in 2 cases.

Bacillus pseudodiphtheriæ was found in combination with *Streptococcus pyogenes*, once with *Bacillus pyocyaneus*, and twice with the *Staphylococcus aureus*.

"Cases cultured on the third or fourth day of discharge show the *Staphylococcus aureus* in many instances. A vaccine prepared of this organism usually gives good results. A week or ten days later it is often replaced by the *Bacillus pseudodiphtheriæ*, or this organism is found in addition.

"It may be well to add here a few words in explanation of the term 'pseudodiphtheriæ.' We are aware that many opinions exist on what should be thus named. We apply that term here to a solid type of diphtheria-like organism resembling some of the solid types of true diphtheria bacilli, but without virulence or toxicity when tested in a reliable manner by animal inoculation.

"We have frequently encountered, isolated, and cultured a short, thick, solid bacillus having rounded ends, with slightly marked median band, characteristic of the *Bacillus hofmanni*. We could never foretell by microscopic examination alone whether solid types of diphtheria-like bacilli were or were not virulent, but relied on an animal test for such information. We believe that a true pseudodiphtheria bacillus exists which belongs to the family of diphtheria bacilli, but have never been able to recognize it with confidence by mere microscopic examination. Twenty-two of the cultures were tested by guinea-pig inoculation and found negative. Two additional cultures, isolated from discharging ears in the diphtheria wards, produced most virulent toxins. Therefore, we believe that the presence of diphtheria-like organisms in the ear can be determined by microscopic examination, but only an animal test can determine whether or not the organisms possess virulence and are a menace to public health. The presence of this organism in 57 per cent. of the cases shows its important position in the etiology of otitis media and its relation to diphtheria of the ear.

"The *Bacillus pyocyaneus* was found in 20 per cent. of cases discharging for four weeks or longer. This organism is believed by many to be a practically harmless saprophyte, feeding on tissues killed by some other organism. In 10 per cent. of our cases this was found alone or in combination with some other organism as early as the third to fourteenth day of discharge. The results of its vaccine were satisfactory in these early

cases, and while the administration of a vaccine prepared from this organism may have been merely coincident to a rapid cure, yet we cannot agree with those who claim its vaccine to be practically without effect, for we believe that it is at least worthy of trial. On the other hand, of the 15 patients dismissed from the hospital with persistent discharging ears, 13 gave this organism in pure culture and its vaccine did not produce favorable results.

"All of the various groups of streptococci are here listed under one name. A vaccine prepared from this organism gave quick and favorable results each time. It was found alone or in combination in 11 per cent. of cases.

"We prepared and used autogenous vaccines for every case except one. This case was one of ten years' standing, following measles. The patient was admitted with scarlet fever and recovered in a satisfactory manner. He was detained, however, on account of the discharging ears, for although the otitis did not develop during the course of scarlet fever, yet his ear discharge was most likely infected, and therefore it was considered dangerous to dismiss the patient. Repeated cultures yielded the *Bacillus pyocyaneus*. A vaccine produced some improvement. Then a stock culture of *Staphylococcus aureus* and *Bacillus pseudodiphtheriae* was tried. Granulation was rapid and all discharge ceased after the fourth dose. His ears were dry for ten days before dismissal from the hospital.

"The initial dose for the average patient 10 years of age was about as follows:—

	Million.
<i>Staphylococcus aureus</i> and <i>albus</i>	15 to 40
<i>Bacillus pseudodiphtheriae</i>	30 to 50
<i>Streptococcus pyogenes</i>	5 to 10
<i>Bacillus pyocyaneus</i>	50 to 80

"It is well to give a small dose at first and note the extent of the reaction. This reaction will be a good guide for determining the size of the succeeding dose. Doses were repeated every five to eight days. In our earlier cases they were given at shorter intervals, but results did not warrant the continuance of the practice. Succeeding doses were increased by 5 to 10 million if necessary. Following the administration, the majority of patients develop a temperature varying from 100° to 102° F. in about eight hours, gradually reaching normal in twenty-four to thirty-six hours. We have seen the temperature fall a degree or so to subnormal after an injection, reaching normal at the end of twenty-four hours. A second dose should not produce so much fever, and when doses are properly selected, the temperature reactions are quite conspicuous, each being lower than the preceding, as the patient's system is charged with an increasing quantity of opsonins, until finally no fever follows the administration.

"The following table shows the number of doses given to secure a favorable result, or convince one that vaccines were giving no aid:—

16 patients received 1 dose (13 cured; 3 died).
11 patients received 2 doses (10 cured; 1 improved).
15 patients received 3 doses (14 cured; 1 improved).
10 patients received 4 doses (10 cured).
10 patients received 5 doses (9 cured; 1 improved).

- 9 patients received 6 doses (8 cured; 1 not improved).
 4 patients received 7 doses (4 cured).
 4 patients received 8 doses (2 cured; 1 improved; 1 not improved).
 3 patients received 9 doses (3 cured).
 3 patients received 10 doses (2 cured; 1 improved).
 4 patients received 11 doses (1 cured; 3 improved).
 3 patients received 12 doses (2 cured; 1 improved).
 3 patients received 14 doses (1 cured; 1 improved; 1 not improved).
 1 patient received 15 doses (1 not improved).
 1 patient received 16 doses (1 cured).
 1 patient received 17 doses (1 cured).
 2 patients received 18 doses (2 cured).

"At the present we can estimate the value of the vaccine treatment by considering the time required to accomplish a cure under the usual form of treatment and that required under vaccines; also by the number of patients dismissed at the expiration of three to four months with ears still discharging. To determine this the records of the hospital have been studied and the results tabulated (Woody):—

"The table is very important because it compares the percentage of patients who were cured under the usual treatment with those cured under vaccine treatment during an equal number of days:—

	Usual treatment. Cured.	Vaccine treatment. Cured.
1 to 10 days.....	3.24%	22%
10 to 20 "	7.47%	22%
20 to 30 "	11.69%	21%
30 to 40 "	17.86%	8%
40 to 60 "	19.15%	4%
60 to 90 "	9.41%	4%
90 to 120 "	2.28%	1%
Dismissed with ears still discharging ..	13.96%	15%
Died, ears still dis- charging.....	14.94%	3%

Number of cases admitted to Scarlet-fever Hospital from June 1, 1907, to June 1, 1909, 2,537.

Number of cases of suppurative otitis media developing during this period, 308, or 8.2 per cent.

"This table demonstrates that under vaccine treatment 21.99 per cent. of cases are cured in from one to thirty days as compared with 7.46 per cent. under usual treatment in the same period of time.

"Of the 15 patients receiving vaccine treatment and dismissed with ears still discharging, 1 was 'running' six weeks, and 5 from twelve to fourteen weeks before vaccine treatment began:—

4 received vaccine treatment on fifth to twelfth day of discharge.

5 received vaccine treatment on the fourteenth to twenty-eighth day of discharge.

1 received vaccine treatment during sixth week of discharge.

5 received vaccine treatment during twelfth to fourteenth week of discharge.

Todd and Western (Practitioner, vol. lxxx, p. 703, 1908) treated 3 patients with middle-ear disease, 1 of which was caused by mixed staphylococcus and tuberculous infection. The other 2 were apparently pure tuberculous infections. The results were successful in all 3 cases.

Magruder and Webb (Laryngoscope, xvii, 879, 1907) reported a case of **pneumococcus infection** of the middle ear with beginning intracranial complications. Two injections were sufficient to cure the condition. Hamilton (Jour. Inf. Dis., vol. iv, p. 313, 1907) treated 7 cases of **otitis media following scarlet fever** with a vaccine containing a pseudodiphtheria bacillus. No advantage could be claimed for the vaccine.

Levy (Ann. Otol. Rhin. and Larynx, xviii, 18, 1909) has collected 48 cases of otitis media. In 32 of the patients treatment resulted in cure, 7 were recorded as improved, and 9 not improved. Striking results were secured in **unhealed mastoid cases**.

McDonald (Jour. A. M. A., vol. liv, p. 966, 1910) reports 3 cases in which the staphylococcus and a short bacillus were found. A cure resulted in 2 cases and failure in 1. Jacobs (Cleveland Med. Jour., vol. ix, No. 2, p. 114, 1910) found staphylococci, streptococci, and the *B. coli* in 6 cases; 2 of the patients were cured and 4 improved. Sill (Med. Record, vol. xxviii, No. 6, p. 299) has treated various bacterial infections in infants and young children. There were 37 cases of otitis media; 28 of these were cured; 10 were improved, and 1 was not improved.

Da Costa ("Trans. of the Assn. of Amer. Phys.," vol. xxi, pp. 259-268, 1910) reports the experience at the German Hospital in Philadelphia, in the treatment of certain bacterial affections mainly of a surgical character during a period of six months. He states that of all the local suppurations dealt with **suppurative otitis** proved the most resistant and stubborn, although an occasional brilliant result from a minimal dose of vaccine was observed. In 6 of the 11 cases treated the ear discharge had been absent for over six to twelve months after inoculations were discontinued. In 2 cases erratic relapses were noted and in 3 there was no improvement whatever. The average course of treatment lasted forty-one days and the dosage in favorable cases ranged from 50 to 2600 million bacteria.

PYORRHOEA ALVEOLARIS.

Chronic suppuration of the alveolar margins, pyorrhœa alveolaris, also known as Rigg's disease, may with advantage be treated by means of vaccines prepared from the infecting organisms isolated from the pus.

Goadby (Lancet, p. 1875, 1909) divides the disease into four types. These types possibly constitute two different disease entities.

Type I.—The gums and teeth appear perfectly normal and the gums show slight depressions between individual teeth. Very careful examination often reveals the presence of pus, and X-ray plates will show a distinct loss of bony tissue.

Type II.—A condition characterized by easily bleeding gums which are slightly detached from the teeth. There is a great increase of the interdental space, with loss of interdental bone which becomes softer.

Type III.—The hypertrophied gums have become shrunken, but there is a marked injection of vessels passing by over the buccal surface. The bones have become rarefied not only between the teeth, but also in the anterior and posterior surfaces of the alveolar plate. The mucous glands may also be infected.

Type IV.—The teeth are all loose in their sockets. The alveolar process has become absorbed; the gums are boggy; sinuses may be present and, as a rule, there is mild fetor of the breath.

Following this classification, Goadby tabulates the cases he has treated (with their general symptoms, his bacteriological findings, and the results of vaccine treatment) as follows:—

CASES WITH SLIGHT LOCAL SYMPTOMS OF TYPE I.

(No generalised infection of gum margins or alveolus; local infection between contiguous teeth; pus small in amount. Gums pale but normal in appearance.)

Case.	General symptoms.	Organisms isolated.	Opsonic index.	Result of treatment.
1	Slight anemia; acne; occasional diarrhea; "indigestion."	Staphylococcus albus.	0.8	Cured.
2	Moderate anemia; loss of weight; constant malaise.	Pneumococcus.	0.5	"
		Micrococcus catarrhalls.	0.7	
	Anemia; recurrent ulceration of buccal surface of cheeks.	Streptococcus longus.	0.4	
4	Desquamation of palmar surface of hands; toxemia.	Micrococcus catarrhalls.	—	"
		Streptococcus longus.	—	
5	No general symptoms.	Staphylococcus citreus granulatus.	4.0	"
6	Recurrent facial neuralgia, paroxysmal.	Diphtheroid bacillus.	0.6	Relieved.
7	Rheumatoid arthritis; fever.	Catarrhalls type.	0.7	Refused treatment; died.
		Saccharomyces neoformans.	2.2	
8	Chronic rheumatism, knee, shoulder, and wrist joints.	Streptococcus longus.	0.7	Relieved.
9	Toxemia; anemia	Diphtheroid bacillus.	0.6	Cured.
10	Chronic pharyngitis; anemia.	Staphylococcus albus.	2.0	Improved; relapsed.
		Staphylococcus citreus granulatus.	0.7	
11	Rheumatoid arthritis, hands and wrists; anemia.	Staphylococcus aureus.	0.7	Relieved.
		Streptococcus.	3.0	
12	Recurrent aphthous ulceration of cheeks and tongue.	Streptococcus longus.	0.6	Cured.
13	Constipation, alternating with diarrhea; toxemia.	Streptococcus longus.	0.7	Relieved.
		Staphylococcus citreus granulatus.		
14	Persistent headache; nausea; anemia; weakness of flexors of wrists and fingers.	Pneumococcus.	2.7	Cured.
		Staphylococcus aureus.	0.3	
15	No general symptoms; large hard diffuse swelling outer angle of mandible.	Diphtheroid bacilli.	0.8	"
16	No general symptoms.	" Bacilli."	1.6	"
17	General malaise; toxemia.	" Bacilli."	0.4	"
18	Acute paroxysmal neuralgia.	Diphtheroid bacillus.	0.4	Much improved.

CASES WITH MODERATE LOCAL SYMPTOMS OF TYPE II.

(Local pus formation; individual teeth unaffected; irregular infection of alveolar process; osteosclerosis as well as rarefying osteitis.)

1	Acne.	Streptococcus longus.	1.8	Cured.
		Bacillus acnes.	0.2	
2	Toxemia; post rhinitis; furunculosis.	Staphylococcus aureus.	0.6	"
		Streptococcus longus.	1.2	
3	Lymphatic enlargement; toxemia; muscular rheumatism.	Streptococcus longus.	0.7	"
4	Toxemia, acute.	Streptococcus longus.	0.5	"
5	Acne.	Staphylococcus aureus.	0.5	Greatly improved.
6	Toxemia; loss of weight; chronic headache.	Staphylococcus aureus.	0.7	Cured.
7	Toxemia (cardiac); herpes of nose.	Staphylococcus aureus.	0.4	"
		Staphylococcus citreus granulatus.	0.6	
8	Toxemia; fever.	" Streptobacillus."	0.5	Relieved.
9	Anemia.	Streptococcus longus.	0.3	Cured.
10	Chronic dyspepsia.	Staphylococcus aureus.	1.4	"
		Saccharomyces neoformans	1.4	
11	Vomiting, toxemia; anemia.	Staphylococcus aureus.	0.6	"
12	Anemia; headache.	Pneumococcus.	—	"
13	No general symptoms.	Streptococcus longus.	0.7	Relieved.
		Staphylococcus albus.	2.0	
14	"	Streptococcus longus.	2.7	"
		Micrococcus catarrhalls.	0.6	
		Micrococcus catarrhalls.	0.8	Cured.
15	Anemia; general malaise.	Staphylococcus aureus.	0.8	
		Streptococcus longus.	0.9	

CASES WITH SEVERE LOCAL SYMPTOMS OF TYPE III.

(General pus flow from alveolar margins; loosening of teeth; absorption of alveolus; bleeding of gums; abscess formation.)

Case.	General symptoms.	Organisms isolated.	Opsonic index.	Result of treatment.
1	Toxemia; gastrointestinal.	{ Streptococcus. Staphylococcus albus. Micrococcus catarrhalis.	{ 0.7	Relieved, but relapsed.
2	Toxemia.	{ Staphylococcus albus. Staphylococcus citreus granulated.	{ 0.6 0.5	Relieved.
3	Toxemia; diarrhea.	{ Staphylococcus aureus. Streptococcus longus.	{ 0.5 1.3	Cured.
4	Anemia; nausea.	Micrococcus catarrhalis.	0.3	{ Relieved, but relapsed.
5	Anemia.	{ Micrococcus catarrhalis. Streptococcus longus.	{ 0.5 1.7	Cured.
6	Gastrointestinal; cardiac.	{ Staphylococcus albus. Diphtheroid bacillus (septus). Staphylococcus aureus.	{ 0.5 3.0 0.8	"
7	Severe toxemia, anemia, prostration.	{ Staphylococcus aureus. Streptococcus longus.	{ 0.8 3.5	"
8	Insomnia; dyspepsia; secondary neurasthenia.	Pneumococcus.	0.4	"
9	Chronic toxemia; breathlessness; anemia.	Micrococcus catarrhalis. Staphylococcus aureus.	1.0 0.3	"
10	General weakness; pharyngitis; glossitis; acute toxemia.	Micrococcus catarrhalis. Micrococcus catarrhalis (?). Saccharomyces neoformans.	1.1 0.6 0.6	"
11	Gastrointestinal; much diarrhea; toxemia.	{ Staphylococcus aureus. Streptococcus longus.	{ 0.6 1.7	Not treated; developed ulcerative colitis.
12	Toxemia; rheumatoid arthritis.	{ Staphylococcus aureus. Pneumococcus.	{ 0.5 2.3	Relieved; still under treatment
13	Toxemia; pharyngitis, vomiting; "neuritis" of arm.	Streptococcus longus.	0.6	Cured.
14	Toxemia; obstinate constipation; anemia; secondary neurasthenia.	Saccharomyces neoformans. Staphylococcus aureus.	0.7 0.8	"
15	Lymphatic leukemia.	Bacillus necrosis.	—	Died.
16	Acute toxemia; fever; vomiting; anemia.	Staphylococcus aureus.	2.6	Cured.
17	Anemia; chronic nausea; toxemia; wasting.	{ Staphylococcus aureus. Pneumococcus.	{ 0.8 0.6	"
18	Acute facial neuralgia; toxemia; neuroedema.	{ Staphylococcus aureus. Streptococcus longus.	{ 0.6 0.7	"

Bacteria are present in the discharge in great number and variety. These bacteria must be constantly swallowed and from the hypertrophied gums bacteria and their products may readily enter the bloodstream. The consequence is frequently general infection and systemic intoxication. The various organic and functional disturbances associated most often with pyorrhœa alveolaris are: anemia of a mild type; gastrointestinal conditions of a toxic nature, frequently associated with neurasthenia, pigmentation of the skin, acneiform eruptions, mild furunculosis, chronic rheumatism pains and joint swelling, pemphigus, recurrent stomatitis with small painful ulcers. Depression often amounting to melan-

cholia, general malaise, and fatigue are common symptoms.

For ascertaining the kind of bacteria present in the pus much can be learned by films stained either by Gram's or Leishman's method. The following bacteria can be readily recognized by their morphological forms: *Leptothrix racemosa* of Vincentini, the *Bacillus fusiformis*, the three varieties of mouth spirochetes, a large number of organisms belonging to the diphtheroid group, diplococci, streptococci, streptobacilli, and yeasts. Various forms of leptothrix and the *Bacillus necrosis* are also found.

The organisms are cultivated on suitable media, and the bacteria considered as the causative agents of the disease are used in making the vac-

cines. The most common bacteria found are the streptococci, the pneumococci, and the *Staphylococcus aureus*. Goadby (Lancet, p. 877, Dec. 25, 1909) has reported finding the *Saccharomyces neoformans* in 4 of his cases. Eyre and Paine (Odontol. Sec. of the Royal Soc. of Med., Nov. 22, 1909) have reported that the *Micrococcus catarrhalis* was a prominent organism. It occurred alone in 15 cases and in conjunction with the streptococcus, pneumococcus, and *Staphylococcus aureus* in the others of a series of 33 cases.

Whenever possible autogenous vaccines should be prepared. The choice of a stock vaccine should be based upon a very careful bacteriological examination. The best results seem to have been obtained with comparatively small doses (7 to 50 million) administered at intervals of seven to ten days. Constitutional disturbances are rare; occasional vomiting, acute headache, and general malaise may be noted. In this condition the mouth is a septic cavity; the teeth are coated with tartar and impregnated with organisms which must necessarily re-infect the gums. Inoculations cannot be expected to attack these superficial bacteria; neither can they be expected to remove dead tissue. Local surgical treatment and antiseptic mouth-washes are therefore indispensable accessories.

W. R. Williams (Amer. Jour. Med. Sci., vol. i, p. 665, 1911) has reported favorable results in treating 8 patients afflicted with pyorrhœa alveolaris. He used comparatively large doses of vaccine (7 to 90 million). Doses were given at weekly intervals.

Medalia (Bost. Med. and Surg. Jour., Sept. 14, 1916) relies entirely on

vaccines and records the fact that many cases in which the emetine treatment fails, are cured by the former.

Joseph Head (Trans. Amer. Assoc. Immunol.; Med. Rec., July 13, 1918), who has had greater experience in this connection than probably anyone, states that he formerly gave large doses of mixed germs. He found, however, that some patients got undesirable symptoms with a dose as low as 30,000, and he has proved that the tolerance of some patients should be carefully ascertained. He concludes that it is better to keep the injection below the point of getting reactions. He now begins with small doses, which, if borne well, are increased. Reactions are of various types, and sore throat and colds are often typical reactions. A dose just short of a reaction gives the best final result.

LIPOVACCINES.

In an address before the American Public Health Association (Med. Record, Jan. 18, 1919), Colonel Eugene R. Whitmore, of the U. S. Army, reviewed the reasons which led to the introduction of these agents. In using bacterial vaccines in protective inoculation, the use of a rather large amount of bacterial material is required to obtain practical protection. With the saline suspended vaccines, it is necessary to give the vaccine in several doses, as the general reaction is severe if the entire amount is given at one time. The necessity of giving repeated doses makes it difficult to carry out protective inoculation on a large scale, even when only one disease is considered. When attempt is made to vaccinate against several diseases, the repeated doses render such vaccination impossible. The body can elaborate antibodies against sev-

eral pathogenic bacteria at the same time; but when attempt is made to include more than one organism in a saline vaccine, the dose of each organism has to be reduced below what was considered necessary to give protection. Another objection to saline suspended bacterial vaccines is that there is rapid autolysis of the organisms in the saline solution, and it is not advisable to use the vaccine after it is over three or four months old.

French investigators have shown that it is possible to inject large amounts of bacterial material suspended in oil, without producing severe general reaction. This is due to the slow absorption of the bacterial material in the oil, and to the detoxifying action of the oil. They also showed that the immunity response was as good after injection of the entire amount of bacterial material at one dose suspended in oil as when it was injected in divided doses suspended in saline solution. They found moreover, that the bacteria remained in the oil for at least eight months without undergoing any change. The French investigators obtained satisfactory results with a T. A. B. vaccine suspended in oil; and they gave the name "lipovaccine" to these vaccines.

In the United States Army, a number of lipovaccines have been prepared; and the triple typhoid lipovaccine is now the official vaccine in the service. A pneumococcus lipovaccine is being used, and meningococcus, dysentery, cholera, plague, and streptococcus lipovaccines have been prepared and tried out. Lipovaccines have the advantages that the entire amount of bacterial material can be given at one dose, without severe

general reaction, and the immunity response is at least as good as where the bacterial material is given in divided doses suspended in saline solution. The lipovaccines keep for at least eight months.

SUMMARY.

In a lecture on the lessons of the war, Sir Almroth E. Wright (*Lancet*, Mar. 29, 1919) stated that it has taught 2 great lessons in immunization. It has taught the surgeon that if he provides the requisite conditions—and he does provide them when he excises all devitalized and heavily infected tissues and brings together the walls of the wound—the protective mechanism of the body can, without any antiseptics, deal successfully with every kind of infection. Experiments with leucocytes—and experience with retarded suture (where we can count on emigration into the wound) have conclusively shown that leucocytes can kill, and that one can successfully close upon streptococcic infections.

The second great lesson of the war has been learned in connection with antityphoid inoculation. The signal success of that procedure has made it manifest to everybody that the natural powers of resistance of the human body can be powerfully reinforced by inoculation.

As regards vaccine treatment in every form of infection a certain quota of unequivocal successes may be credited to the method, and especially successful results have been obtained in **furunculosis** and acute inflammatory **syctosis**; in "poisoned wounds"—meaning by that localized cellulitis set up by a **streptococcus infection**; in streptococcal infections taking the form of lymphangitis, in

erysipelas; in tubercular adenitis, tubercular joint infections, tubercular dactylitis, tubercular orchitis, and tubercular affections of the eye, especially in phlyctenules of the conjunctiva; again in bronchitis, in coli cystitis, and gonorrheal rheumatism. The most dramatic and convincing—convincing because here no other therapeutic measures are employed as adjuncts—are the successes obtained in streptococcal lymphangitis, in streptococcal cellulitis—those cases which have already been incised without striking benefit—and in conjunctival phlyctenules.

Analysis of the successes and failures of vaccine therapy the following points come out quite clearly:—

(1) It is generally unsuccessful where the infection—as in phthisis—is producing constitutional disturbance and recurring pyrexia.

(2) It is also generally unsuccessful where we have to deal with unopened abscesses, or sloughing wounds with corrupt discharges.

(3) In long-standing infections vaccine therapy is much less successful than in recent infections.

[The use of vaccines in the various diseases is also considered with the latter, under Treatment. See Index.—Ed.]

A. PARKER HITCHENS,
Philadelphia.

BACTERIURIA.—If freshly voided urine free from pus is turbid, the turbidity being due entirely to the presence of micro-organisms and not to urinary salts, this condition is referred to as "bacteriuria." In giving this definition, L. E. Schmidt (Ills. Med. Jour., xxxvi, 188, 1919) states that there is a class of cases of bacteriuria in which pus is found in the urine because of the presence of an inflammatory condition. In the vast majority of cases seen in routine practice the urine contains pus in varying amounts and this pus may

or may not have a bearing on the bacteriuria. Take, for instance, the so-called *colon-bacillus infections* of the kidneys. In these, pus and blood are found in the urine as well as large numbers of bacteria. In some other conditions also the bacteria may descend from the upper urinary tract but the pus may come from some chronic inflammatory condition of the urethra or adnexa.

Another class of cases are those in which the presence of pathologic conditions outside of the urinary tract has been definitely demonstrated and the bacteria, pus, and blood make their entrance into the urinary stream from these foci. There is likewise a group in which there is a complete absence of demonstrable lesions and pus, and the turbidity of the urine is due entirely to the presence of bacteria.

It is highly desirable to ascertain where the bacteria enter the urinary stream. In the acute infectious diseases, such as *typhoid fever*, it is not at all uncommon to find the true bacteriuria due entirely to the bacillus typhosus, pus and blood being absent. Again, in chronic *pulmonary tuberculosis*, investigations have shown that in a fair percentage of cases the bacillus tuberculosis is eliminated through the kidneys constantly. The same is true in many other infectious diseases. At any time the bacteria may cause an inflammatory disease of the urinary tract which may be the only involvement or may be concomitant with the bacteriuria. Occasionally bacteriuria has been noticed following *instrumental treatment* or examination and therefore it has been concluded that the point of entrance was an injury.

Bacteria are pathogenic at certain times and non-pathogenic at others, and sometimes cause marked inflammatory reaction and at others are apparently not injurious to the same tissue. The *colon bacillus* may, for example, cause most violent attacks of true infection of the kidneys, high temperature, chills, and most pronounced general and local signs and symptoms.

The symptoms of bacteriuria vary. In some patients local and general symptoms are practically absent while in others there may be headache, backache, a feeling of extreme fatigue, and perhaps a rise in temperature and chills. Others, again, show

only local urinary symptoms, or both general and local symptoms. of varying severity.

Systemic and local treatment, including vaccines, is helpful. Nolf (N. Y. Med. Jour., Dec. 20, 1919) found progressive intravenous vaccination very satisfactory.

BARIUM.—The metal barium, which is not used medicinally, occurs in nature as a sulphate termed barite, and as a carbonate: witherite. It is the most poisonous of the three common alkaline earths.

PREPARATIONS AND DOSE.—

The only one used to any extent in therapeutics of the many salts of this metal is the barium chloride, *barii chloridum*, a white, crystalline salt having a bitter, disagreeable taste. The dose is $\frac{1}{10}$ to $\frac{1}{2}$ grain (0.006 to 0.03 Gm.). Experience has shown, however, that these doses are too large, and the best results are obtained with doses of from $\frac{1}{40}$ to $\frac{1}{10}$ grain (0.0015 to 0.006 Gm.). It is readily soluble in water, fairly so in alcohol, though hardly at all in absolute alcohol.

PHYSIOLOGICAL ACTION.—

The main action of barium is on the cardiovascular system. It increases, as does digitalis, the power of the cardiac contractions, but reduces their number. It enhances also the tonicity of the blood-vessels, causing an increase of the vascular tension. The tracings of barium and digitalis are strikingly alike. Moreover, its effects are independent of the central nervous system, another point of similarity. It presents the peculiarity of being able to restore the contractions of the heart when these have been arrested by muscarine or chloral. Large doses first stimulate the heart's action, but this is soon converted into depression,

with irregularity, weakness, and later on imperceptibility of the pulse. The blood-pressure is influenced in the same way, a rise being soon succeeded by a more or less sudden fall, according to the dose administered. As recently (1909) shown by Meyer, barium passes out mainly with the feces.

BARIUM POISONING.—Excessive or toxic doses tend to give rise to symptoms of cardiovascular failure, the pulse being weak, slow, and irregular. Besides these effects, however, there appear phenomena due to violent excitation of the gastrointestinal musculature, viz., vomiting and diarrhea, soon followed by intense weakness, dyspnea, hypothermia, albuminuria, hemoglobinuria, and, the latter increasing gradually until asphyxia is approached, death following after a few clonic convulsions. After death, which has been attributed to the formation of multiple emboli, there is early rigidity, with lesions in most organs, particularly in the kidneys, in which tubular hemorrhages are frequent, with granulofatty infiltration of the secretory epithelium. In favorable cases a temporary paresis or virtual paralysis may occur.

Owing to the toxic symptoms which sometimes occur after taking large doses of bismuth mucilage in X-ray examinations, a perfectly harmless substitute for bismuth has been sought. Barium sulphate has been warmly recommended for this purpose; it is insoluble in water and in acids, and trials made on man have demonstrated its harmlessness, as it passes through the stomach and intestines unchanged, and there is no unpleasant action whatever. Only a pure product should be employed, however. It must be absolutely free from soluble salts of barium, the presence of which, even in

small quantities, produces toxic effects. Great care should be taken *not to use the barium chloride or the barium carbonate* which becomes converted in the stomach into the former very poisonous salt.

TREATMENT OF BARIUM POISONING.—This consists in administering **magnesium sulphate** in **white of egg**, after administering an **emetic** if there is any reason to believe that any of the poison is still present in the stomach. As barium chloride is absorbed slowly from the intestine, it is also advisable to administer a **saline purgative**. **Heat** and **stimulating measures** are important adjuncts.

Bardet reported a case in which $2\frac{1}{2}$ grains (0.016 Gm.) in divided doses sufficed to cause death, while of 2 other cases mentioned in the dispensatory 1 case survived after taking 60 grains (4 Gm.), and the other died after taking 300 grains (20 Gm.). Phillips states that, while the minimum fatal dose is commonly put at 1 dram (4 Gm.), this dose has caused death in seventeen hours.

Case in which $1\frac{1}{2}$ drams (6 Gm.) of barium chloride had been taken by mistake. By noon the next day, on the patient's arrival at the hospital, his condition was as follows: Pulse, 64; temperature, $95\frac{3}{4}^{\circ}$; respiration, 30, shallow and interrupted. Patient could swallow with difficulty; extreme nausea, but no vomiting; after a preliminary violent attack of diarrhea, there was no bowel movement for six hours; not a muscle of his body could be moved, but control of sphincters was normal. Under active treatment, recovery occurred. E. G. Edwards (Jour. Amer. Med. Assoc., Jan. 1, 1910).

THERAPEUTICS.—Da Costa held that barium was advantageous in cardiac disorders, including **valvular diseases** in which digitalis was in-

dicated; he found that it reduced the cardiac distress and increased vascular tone and diuresis, while, moreover, it could be administered a long time without disordering the stomach. The prevailing view at the present time is that digitalis is superior to barium in every respect. It has been recommended, however, for the milder degrees of **cardiac insufficiency**, especially with low blood-pressure. This applies also to failure of the circulation in acute diseases, **pneumonia** for example. So high an authority as Phillips, of London, speaks favorably of barium chloride in **mitral disease** and **cardiac dropsy**, but in very small doses, $\frac{1}{40}$ grain (0.0015 Gm.) three times daily. Hare and Carpenter also favor its use, the latter observer emphasizing the advisability of using only small doses, *i.e.*, 30 minims (2 Gm.) of a 1 per cent. solution, gradually increased to 2 drams (8 Gm.).

McCall Anderson has employed the barium sulphide for the removal of **surplus hair**, "one part being made into a paste with four parts of zinc oxide and a little water; this should be left on the part for about three minutes and then washed off. It should be prepared only as required for use" (Phillips). Barium chloride has been found useful in **chlorosis**, especially when the blood-pressure is low.

C. E. DE M. SAJOUS
Philadelphia.

BELLADONNA.—Belladonna is a solanaceous plant, the *Atropa belladonna*, or deadly nightshade, which is indigenous to southern Europe and central Asia. The leaves and root are used in medicine, and also its important alkaloids, *atropine*, which occurs in the plant in combination with

malic acid as a bimalate; *belladonnine*, analogous to atropine, obtained from the mother-liquor after atropine has crystallized out, and *hyoscyamine*, practically identical with atropine.

PREPARATIONS AND DOSES.

—The official preparations of belladonna are the following:—

Belladonna leaves, or *belladonna folia*, which have a slightly bitter and disagreeable taste. Dose, 1 to 5 grains (0.065 to 0.32 Gm.).

The leaves in turn are used to prepare:—

The extract of belladonna leaves, or *extractum belladonna foliorum*. Dose, $\frac{1}{10}$ to $\frac{3}{4}$ grain (0.0064 to 0.048 Gm.).

The tincture of belladonna leaves, or *tinctura belladonna foliorum*. Dose, 5 to 15 minims (0.3 to 1.0 c.c.).

The belladonna plaster, or *emplastrum belladonna*, composed of 3 parts of extract of belladonna leaves to 7 of adhesive plaster.

The belladonna ointment, or *unguentum belladonna*, which contains 10 parts of extract of belladonna leaves, 5 of dilute alcohol, 65 of benzoinated lard, and 20 of hydrous wool fat.

The root, *belladonna radix*, is used to prepare:—

The fluidextract of belladonna root, or *fluidextractum belladonna radices*. Dose, 1 to 3 minims (0.06 to 0.18 c.c.).

The belladonna liniment, or *linimentum belladonna*, composed of fluidextract of belladonna root, 950 parts, and camphor, 50 parts.

Of the active principles the following preparations are employed:—

Atropine, or *atropina*, occurs in the form of white, amorphous, acicular crystals or powder having an acrid, bitter taste. It is soluble in 130 parts

of water, 3 of alcohol, 16 of ether, 4 of chloroform, and 50 of glycerin. Dose, $\frac{1}{120}$ to $\frac{1}{60}$ grain (0.0005 to 0.001 Gm.).

Atropine sulphate, or *atropina sulphas*, which occurs as a white powder having an intensely bitter and disagreeable taste. It is very soluble in water, soluble in 6.2 parts of alcohol, in 694 of chloroform, and 2270 parts of ether. Dose, $\frac{1}{120}$ to $\frac{1}{60}$ grain (0.0005 to 0.001 Gm.).

INCOMPATIBLES.—Atropine is chemically incompatible with the alkalies, tannin, and the salts of mercury; it is physiologically incompatible with morphine (opium), pilocarpine, muscarine, aconitine, and eserine (physostigmine).

The action of belladonna and its alkaloids is antagonized by muscarine and partly so by pilocarpine, physostigmine, and aconite. Opium and its analgesic derivatives oppose its action on the cerebrum, pupil, and respiration.

The conclusions from 225 tests made at the Pharmacology Institute of the University of Utrecht are that a given amount of atropine is able to neutralize the action of physostigmine in the proportions of 1 to 1500 up to 1 to 1,500,000. (Nederlandsch. Tijdsch. v. Geneeskunde, Sept. 29, 1917).

PHYSIOLOGICAL ACTION.—

The physiological action of belladonna is that of its main alkaloid atropine. We shall first describe the manner in which the various systems are influenced by the drug, and then review at length the clinical phenomena witnessed when it is used in therapeutic doses.

Nervous System.—Atropine has no particular effect on the brain and spinal cord when administered in

therapeutic doses, but it depresses certain peripheral nerve-endings, especially those in the heart and secretory organs, such as the salivary and sudorific glands, thus reducing their secretions: the saliva and sweat in the examples given. The nerve-endings in certain involuntary muscles, such as the constrictor of the iris, the ciliary muscles, and the muscular coat of the bronchial tubes, are likewise depressed. In excessive doses it excites the brain, producing delirium, with hallucinations, incoherent speech, laughter, and motor restlessness, these effects being followed, after a time, by quietude and stupor. The medulla and cord are also stimulated and then depressed by atropine, but these effects are less marked than those on the brain.

The effects on the nervous system are often overlooked. It happens occasionally that because of the attendant delirium a subject is rushed to an asylum. In any suspected case any suspicious beverage or medicine in evidence can be used to test, a drop of this being instilled into a cat's eye. This failing, a drop of the patient's urine may serve the same purpose. Hunziker (*Correspond. Blatt f. schweizer Aerzte; Druggist Circular*, Dec., 1916).

Circulation.—In moderate doses atropine depresses the vagal nerve-endings of the heart, while strongly stimulating the vasomotor center and also, but to a slight degree, the heart-muscle. As a result there occur increase of the pulse rate and a rise of the blood-pressure. Toxic doses cause a secondary depression of the circulation. Another effect observed under the influence of therapeutic, and very often of toxic, doses is a scarlet flushing of the skin affecting first the face and neck and then the

chest. This is due to dilatation of the cutaneous vessels, and is believed to be of central origin, since cutting of the sympathetic prevents this phenomenon. This superficial dilatation is not sufficient, however, to counteract the rise of blood-pressure caused by the constriction of the internal vessels. Nor is it accompanied by sweating, since the sweat-glands are paralyzed early in the course of the process.

The writer reached, after an experimental study, the general conclusion that at the outset atropine causes augmentation of the excitability of the cardio-inhibitory elements of the vagus. This increased excitability is not merely apparent but is genuine. Petzetakis (*Presse méd.*, Dec. 4, 1916).

Respiration.—Full therapeutic doses stimulate the respiratory center, causing rapid and deep breathing. Under the influence of poisonous doses, the center becomes secondarily depressed, causing death from asphyxia.

Any respiratory stimulation due to atropine is to be explained by (1) the increased "dead space" or dilatation of the bronchi, and (2) increased metabolism. The metabolism being increased, the respiratory volume increases to rid the body of CO₂ produced, and for a unit of CO₂ eliminated, the respiratory volume increases because of an increased "dead space." Higgins and Means (*Jour. of Pharm. and Exper. Therap.*, July, 1915).

Eye.—Taken internally in full doses or locally applied, atropine causes marked dilatation of the pupil, with loss of the light reflex and a tendency to increased intraocular tension. Paralysis of accommodation is also produced. These effects are due to depression of the oculomotor

endings in the circular muscle of the iris and ciliary muscle.

Secretions.—Atropine reduces or actually checks the activity of all structures, excepting the kidneys. The saliva, gastric juice, sweat and mucous secretions of the respiratory tract are the most strongly affected; the pancreatic juice and bile, to a less extent. The drug finally paralyzing the endings of secretory nerves, it causes dryness of the mouth, thirst, anorexia, dryness of the skin, elevation of the superficial temperature, and hoarseness. In nursing women the mammary secretion is reduced, though not entirely checked, by atropine.

Involuntary Muscles.—In very small doses atropine increases slightly intestinal peristalsis, probably by depressing the inhibitory (splanchnic) nerve-endings in the intestinal walls in the same way that it depresses the vagal endings in the cardiac muscles. Full doses, on the other hand, exert a depressant, or at least a controlling, effect on involuntary-muscle tissues in general. In the case of the intraocular muscles, the muscular coat in the bronchial tubes and esophagus, this effect is due to paralysis of the terminals of the motor nerves distributed to these muscles. In the case of the stomach, intestine, bile-ducts, ureters, uterus, and bladder, however, the nervous control of the involuntary muscle-tissue is not affected. Small doses of the drug tend, under normal conditions, rather to stimulate muscular activity in these organs than to depress it, but, when abnormal stimuli to contraction of the muscle occur which tend to produce spasm, these small doses depress the muscles and thus tend to prevent

spasm. In toxic doses or when applied locally atropine paralyzes involuntary muscular tissue directly.

Temperature.—Atropine causes a rise of temperature by arresting the action of sweat-glands and thus reducing heat dissipation.

Local Action.—Atropine is practically non-irritating. Used locally in sufficient concentration, it depresses sensory and motor nerve-endings, involuntary-muscle tissue, and also glandular tissues.

[From my viewpoint all the above phenomena which appear confusing, though representing the prevailing classic interpretation of the action of atropine, may be explained without difficulty in the following way: Atropine excites more or less actively the sympathetic center, which in turn governs the *propulsive* activity of the arterioles and, therefore, the volume of blood these minute arteries admit into the capillaries of all tissues. A therapeutic dose of atropine enhances, therefore, the functional activity of a tissue by causing more arterial blood to enter that tissue; it will increase peristalsis for example by admitting an excess of blood into the muscular coat of the intestine. But toxic doses have a different effect: they so excite the arterioles that they cause excessive constriction of the vessels, thus reducing their caliber to such an extent that the blood admitted to the tissues is inadequate to enable them to carry on their function. A toxic dose will thus arrest or inhibit peristalsis by reducing or even arresting the arterial blood admitted to the intestinal muscular coat and likewise the secretory activity of glands by inhibiting the activity of their secreting cells, etc. For further details on this interpretation the reader is referred to my work on the "Internal Secretions," 5th ed., p. 1210. C. E. DE M. S.]

The volume of the normal saliva, its amylolytic power, and the amount and percentage composition of solids secreted remain approximately constant during a continuous period of secretion of 6 or 8 fifteen-minute

periods. If there is any change, it is a very slight falling off of the percentage composition of organic solids and at times of the amylolytic power. Atropine diminishes the amylolytic power of the saliva from 15 to 30 per cent. Both the amount and percentage composition of total solids secreted are greatly diminished by atropine. The decrease is in the organic constituents. E. M. Ewing (*Jour. of Pharmacol. and Exper. Therap.*, Sept., 1911).

Clinical Effects.—These have been so carefully studied by John Harley that his version is presented here with but few changes:—

If the minimum therapeutic dose, $\frac{1}{20}$ grain (0.0005 Gm.), be injected beneath the skin of a healthy adult, there will be noticed, after ten to twenty minutes, a quickening of the pulse, and generally a small increase in volume and power. This change will be very decided if the pulse was previously slow and feeble. The increase in the number of pulse-beats will generally amount to 20 per minute; it will take place suddenly, and attain its maximum within one or two minutes. In about half an hour a gradual decline takes place and the heart soon returns to its usual state, and continues to beat as quickly and powerfully as before. Just as the pulse rises, a slight giddiness is often perceptible. Usually these will be the whole of the symptoms; but in weak and delicate adults, a feeling of dryness of the mouth and throat, and, at the end of an hour or two, a slight dilatation of the pupil, in a subdued light, will be superadded.

When $\frac{1}{60}$ grain (0.001 Gm.) is used, the acceleration of the pulse will be found to range between 20 and 60

beats, the rise being attended by considerable giddiness and waviness of the vision. The patient walks cautiously, and with an inclination to unsteadiness. After twenty to forty minutes he will complain, with some huskiness of voice, of great dryness of the throat and mouth, and the anterior part of the tongue or the whole of the dorsum, excepting a wide margin, will be found dry, brown, and rough. The hard palate, and in many persons the soft palate also, will be perfectly dry and glazed. There will be more or less somnolency, and sometimes a little flushing of the face. The dilatation of the pupils will amount to $\frac{1}{4}$ or $\frac{1}{6}$ inch.

The effects of $\frac{1}{48}$ grain (0.00135 Gm.; a slightly toxic dose) are as follows: After ten or fifteen minutes an acceleration of the pulse of from 20 to 70 beats; no apparent change in volume, but a decided increase in the force of the cardiac contractions and of the arterial tonus; a general diffusion of warmth, a slight throbbing or heaving sensation in the carotids, and a feeling of pressure under the parietal bones; giddiness, heaviness, drowsiness, or actual sleep, with great tendency to dreamy delirium, and, in women, slight occasional startings; complete dryness of the tongue, roof of the mouth, and soft palate, extending more or less down the pharynx and larynx, rendering the voice husky, and often inducing dry cough and difficulty in swallowing; parched lips, occasional dryness of the mucous membranes of the nose and eyes, and increasing dilatation of the pupils. After about two hours the dryness of the mouth is relieved by the appearance of a viscid, acid

secretion of an offensive odor, like the sweat of the feet; the mouth becomes foul and clammy, and a bitter, coppery taste is complained of; but as moisture returns to the mouth, the pulse is observed to fall, and it now rapidly regains its ordinary rate and character. The pupils have now reached their maximum dilatation and measure about $\frac{1}{5}$ inch; but when exposed to bright light, they will still contract to $\frac{1}{6}$ or even $\frac{1}{8}$ inch, according to their original size. Slight elevation of surface temperature is noticed during the action of the medicine, rarely exceeding 1° , and a still less elevation of the internal temperature of the body. No difference will be observed in the rate of the respiration, except (in nervous women) a little emotional excitement on the sudden accession of the giddiness. The breathing will be tranquil, the patient occasionally heaving a deep sigh, and still oftener taking a prolonged yawn, as he sits still in a dull, apathetic or drowsy condition. After the pulse has resumed its ordinary rate, and the mouth has become moist, the giddiness and drowsiness pass off, and the patient appears tolerably lively and brisk in mind and body. But he will himself continue to feel for some hours longer such languor of body and mind as will render him disinclined for, or even incapable of, active bodily or mental exertion. Slight dimness of vision also remains, and the patient is unable to thread a needle, or even to read.

If larger doses be given, there will be superadded a distressing fluttering sensation in the cardiac region, slight delirium; exquisite sensibility of

hearing, and frequent illusions of this sense also; staggering, or complete inability to walk; insomnia, restlessness, and frequently great nervous agitation of mind and body. Nausea and headache are rare and exceptional consequences of the subcutaneous use of atropine, but sometimes follow when it is given by the stomach in full doses.

Certain conditions modify the action of atropine. Children are more tolerant of the drug than adults, and in this respect resemble the lower animals; and while acceleration of the pulse, dilatation of the pupils, and dryness of the mouth are more readily induced in them, cerebrospinal effects—giddiness, drowsiness, sensory illusions, and unsteadiness of gait—are only developed after a very large dose. Pregnancy appears to diminish the activity of atropine. The weak, and those of excitable temperament, are more readily and powerfully influenced than the strong. In renal disease, when the secretion of urine is diminished, or only moderate in quantity, the effects of atropine are readily induced and considerably prolonged; in persons with unusually active kidneys the action of the drug is less pronounced. While atropine in contact with caustic soda and potash is decomposed in the course of two or three hours, these bodies have no power of annulling or even diminishing the action of the alkaloid within the body. Acids have no particular influence on the action of atropine. When administered by the stomach, the action of the drug is sometimes delayed for two hours, and then develops suddenly.

Atropine passes undiminished and

unchanged through the blood, and the kidneys are active in its elimination from the minute that it enters the circulation until it is entirely removed from the body. After a full medicinal dose, between two or three hours are required for this purpose. The presence of atropine in the renal secretion after taking the drug may be demonstrated by dropping one or two drops of the urine within the eyelids of another person or animal at intervals of ten to twenty minutes for two or three hours and noticing its dilating action on the pupils. The atropine may be separated from the urine by shaking the latter with a quantity of chloroform equal to a sixth of its bulk, and separating the chloroform, or allowing it to evaporate spontaneously. The remaining stain is dissolved in a few drops of water, and a drop placed within the eyelids. The $\frac{1}{96}$ grain (0.00067 Gm.) of atropine sulphate (sufficient to kill an infant) may thus be easily detected in the urine.

Atropine in ordinary, non-toxic doses has no striking influence on the eosinophiles of the guinea-pig's blood. In toxic doses there is a diminution of these cells. Herrick (*Arch of Intern. Med.*, May 15, 1914).

The action of atropine in therapeutic doses on the sympathetic nervous system and the circulation is, we have seen, that of a direct and powerful stimulant. During the operation of medicinal doses the heart contracts with increasing vigor, the arteries increase in tone and volume, the capillary system is also stimulated, and a diffused warmth is felt throughout the body. If the dose be excessive, overstimulation is produced and signs of exhaustion are soon manifest.

The skin becomes the seat of a sensation of warmth followed by a temporary blush, and in children and adults of light complexion is sometimes followed by a scarlet suffusion, described by some as a "scarlatinous rash." In persons subject to vascular irritation of the skin the redness remains and its disappearance may be attended with slight roughness and desquamation.

[Harley states that the general effect of atropine on the circulation predisposes to sweating; but other authorities ascribe to atropine a strong inhibitory action over the sweat-glands. We have here another example of the process of primary hyperemia of the sweat-glands and increased secretory activity and of the secondary inhibition—by constriction of their arterioles—of the sweat-secreting mechanism. C. E. DE M. S.]

In its action on the cerebrospinal system the general effects of atropine resemble those of opium in that it is both an excitant and hypnotic, but the soporific effect is less marked, and coma, if it occurs, must be considered a remote consequence rather than a direct effect of the action of the drug. After large doses insomnia and delirium arise and poisonous doses prolong these effects for hours, and coma gradually supervenes. Headache, vertigo, illusions, hallucinations, a busy delirium, and sometimes somnolence are produced by large doses: more or less anesthesia of the sensory centers of the cerebrum. The action on the motor centers and the spinal cord is comparatively slight. The corpora striata participate both in the hypnotic and in the excitant effects. Giddiness and muscular weakness, with inability for exertion, accompany the hypnotic effect, while restlessness and insomnia occur

when the hypnosis is overruled by the excitant action. The spinal cord is least of all affected by atropine.

ATROPINE POISONING.—This may be produced either by the ingested alkaloid itself or by any of the crude drugs containing it, especially belladonna. It can also occur, and frequently does, owing to the large doses dropped into the eyes by ophthalmologists, by absorption from the eye, and also from the skin when, for instance, an excessive quantity of the belladonna ointment is used.

The writer has often observed evanescent erythema of the face, chest, and abdomen follow instillations of 0.5 to 1 per cent. aqueous solution of atropine in children aged between 2 and 7 years. Prostration or delirium, so frequently noted in adults, was never observed. In some children the erythema regularly followed each instillation. Most of the subjects were affected with phlyctenular ophthalmia, arguing a reduced condition of the system. The phenomena were particularly noted during the inflammatory attacks, much less frequently in intervals of quiescence. These accidents became very infrequent when collyria in oil were substituted for the aqueous; if the latter are employed the lachrymal puncta should be compressed with the finger. Colin (*La Clin. Ophthalmol.*, Dec. 10, 1910).

The likelihood of toxic phenomena is greater when the alkaloid is administered hypodermically than when given by the mouth.

The early signs of atropine poisoning, those which denote the so-called "physiological limit," are: dryness of the mouth and throat, with redness and occasionally pain; dilatation of the pupils, with imperfect vision; a rapid, high-tension pulse, and hot, dry skin. These signs indicate that

the drug should not be pushed further. When this limit is exceeded, there appears an erythematous rash resembling that of scarlet fever on the face, neck, and body, often accompanied by dysphagia, a sensation of burning in the throat, and hoarseness, the patient becoming by that time very restless. Acceleration of the respiration, extreme rapidity of the pulse, and muscular inco-ordination, with more or less increase of the reflexes, then develop. A prominent symptom at about this time is delirium, generally with noisy, disconnected talk and hallucinations, occasionally with violent motor excitement, and even convulsions, leading finally to stupor.

[This typifies, in the light of my interpretation of the action of atropine, the period during which it increases violently the propulsive activity of the arterioles, thus driving an excessive quantity of arterial blood into the cellular elements of all organs and causing violent hyperemia of the skin (erythema), brain (delirium), spinal cord, and peripheral sensory elements (convulsions), etc. C. E. DE M. S.]

More or less generalized eruptions not only occur from the internal administration of belladonna or its alkaloid, atropine, but also from absorption through the skin of local applications of the same. The skin does not have to be broken or denuded of epidermis for absorption to take place; the symptoms of poisoning, however, develop much sooner if such is the case. The great majority of the cases exhibit an erythematous or scarlatinat type of eruption, which is more frequently found on the face and the upper portion of the body, but in a fair number of cases the outbreak is generalized. Gangrenous, purpuric, and eczematous eruptions have been reported. Although in a great many instances severe symptoms of poisoning are

present, the eruption may be unaccompanied by other manifestations of drug absorption. Mydriasis is a quite constant phenomenon; in a few cases, however, the pupils were only slightly enlarged, entirely normal, or unilaterally dilated. The prognosis is favorable; only 1 death occurred in this large series of cases. Belladonna or atropine may produce a local eruption from the local irritant effect. F. C. Knowles (*Amer. Jour. Med. Sci.*, July, 1911).

Two cases of belladonna poisoning which presented marked mental excitement. The sudden development of illusions, hallucinations, and delusions in a previously healthy person should always awaken suspicion of a toxic psychosis. M. Allen Starr (*Med. Record*, June 10, 1911).

Three cases of belladonna poisoning in little children, aged respectively 4, 5 and 6 years, due to eating of the purple berries picked by them from fruiting atropia belladonna shrubs, in a public garden. All 3 recovered under appropriate treatment, **gastric lavage** having brought away the berries. Mary E. Joll (*Lancet*, Oct. 7, 1916).

In spite of these alarming symptoms, which may end in death in from five to twenty hours, a fatal ending occurs only in a small number of cases (about 12 per cent.). In the fatal cases the primary respiratory stimulation is followed by depression of the respiratory center; the circulation also fails, and death occurs from asphyxia.

[The functional arrest of the respiratory center is due, from my viewpoint, to the excessive constriction—the second phase of the action of atropine previously referred to—of the arterioles and the resulting ischemia of the center. C. E. DE M. S.]

Several cases have been reported in which belladonna poisoning followed the application of belladonna plasters.

Case of poisoning from belladonna plaster in a healthy man. The plas-

ter, 6 by 4½ inches, had been applied to his back for the relief of pain at about 11 A.M. and by 2 P.M. the patient had become delirious, maniacal, and irresponsible. He had dryness and redness of the skin, the pupils were dilated, the pulse 130, and respiration 40 per minute. The plaster was removed and his condition improved by evening. Two days later the only sign of belladonna poisoning which remained was some dilatation of the pupils. He had no memory of what had occurred. B. G. R. Crawford (*Brit. Med. Jour.*, Aug. 11, 1917).

TREATMENT OF ATROPINE POISONING.—The best antidote is **Lugol's solution** (the liquor iodi compositus). **Tannic acid**, 30 grains (2 Gm.) in water, or vegetable astringents containing it, including **tea**, are also valuable. The first step is to empty the stomach with the **stomach-tube**, or by means of an emetic, such as **apomorphine** ($\frac{1}{10}$ grain—0.006 Gm.) hypodermically if the case is in the first stage. When the asthenic stage is reached, however, **zinc sulphate** ($\frac{1}{2}$ dram—2 Gm.) by the mouth or **mustard** (2 drams—8 Gm.) in lukewarm water is safer. Any of the physiological antagonists of atropine, such as **pilocarpine** or **physostigmine**, may be cautiously given, but only in the early stages. **Morphine** is often recommended as an antidote, but the dose usually given, $\frac{1}{4}$ grain (0.016 Gm.), should not be repeated, since it is not, as generally taught, a true antagonist of belladonna, serving chiefly to prevent or quiet the delirium, which is also relieved by an **ice-bag over the head**.

Morphine does not save life even in mild cases of belladonna or atropine poisoning. When the dose of the latter is sufficient to initiate the paralyzing phenomena in the nervous

system morphine is a dangerous agent. It is especially contraindicated when the case is comatose. Morphine on the whole should not be regarded as antagonistic of atropine. Roch (*Revue médicale de la Suisse romande*, Feb. 20, 1908).

Pilocarpine, $\frac{1}{4}$ grain (0.016 Gm.); or **physostigmine**, $\frac{1}{30}$ grain (0.002 Gm.), may also be employed to counteract the secretory paralysis, cardiac acceleration, and pupillary dilatation caused by atropine—aside from the true toxic effects. During the period of excitement, **ether** or **chloroform** may be required.

Six cases of belladonna or hyoscyamine poisoning, all terminating in recovery. The poison should be removed by **emetics**, followed by **lavage** after an injection of **morphine**. Purgatives and enemas are also useful in case the poison was taken by the mouth. If injected, the place of injection should be cut into and the blood squeezed out. **Potassium permanganate** is said to be a chemical antidote to atropine. The lavage can be done with water tinted with the permanganate to a pale bluish pink; the permanganate can be given internally in spoonfuls of a 0.25 to 0.5 per cent. solution. Husemann recommends administration of **tannin**, and others **iodine** and **potassium iodide**. Morphine is extremely valuable, but it has no action on the heart, and in case of stupor, coma, or paralysis it may do actual harm. In such cases **black coffee**, **camphor**, **caffeine**, **stimulation of the skin**, etc., are indicated. The nervousness and insomnia are best combated by **tepid baths**, and the patient should **drink as copiously** as possible. A large proportion of the atropine poisonings on record were due to carelessness in prescribing. Löbl (*Wiener klin. Woch.*, Bd. xviii, Nu. 34, 1905).

Case of poisoning in a child of 2 years in which there was a scarlet eruption very closely resembling that of scarlet fever. The tempera-

ture was normal; pulse, 180; pupils dilated and did not contract to light. The skin was dry; also the lips and tongue. It was quite clear that the child had taken an aqueous solution of atropine. She was quite nervous and fretful and seemed, by the twitching of the arms and legs, to be on the verge of a convulsion.

Treatment consisted of giving **paregoric**, $\frac{1}{2}$ dram (2 Gm.), which soon quieted the child. It did not seem advisable to give an emetic, as the child had taken the poison some two hours previously. A solution of paregoric was left containing 15 minims (1 c.c.) to the dose to be given every two hours if the child became very restless. Two hours later the writer was called again, and remained all night at the bedside, and despite the administration of 15 drops (1 c.c.) of paregoric every hour the child did not sleep till near morning. Then he started with 2-grain (0.13 Gm.) doses of **tannic acid** every two hours. The child soon fell into a quiet sleep, and in twenty-four hours from taking the drug was in a normal condition. C. A. White (*Med. World*, Oct., 1911).

In a study of the action of the blood on atropine, the writers found that the substance in rabbit serum which annuls the toxic action of atropine is of the nature of a ferment. The reaction was positive in 30 per cent. of 10 patients with exophthalmic goiter and in 15 per cent. of 20 with ordinary goiter; it was never found in the 20 persons with apparently normal thyroids. Döblin and Fleischmann (*Zeit. f. klin. Med.*, lxxvii, Nu. 3-4, 1913).

During the second stage, that of circulatory and respiratory depression, **external heat**, stimulants, such as **caffeine sodiobenzoate**, **strychnine**, **digitalin**, etc., are indicated. **Artificial respiration** and **hypodermoclysis** of **saline solution**, or better **intravenous infusion** of the latter, are of great assistance, especially when we take into account the tendency to recovery

if life can be prolonged long enough by artificial means.

Retention of the urine being the rule in these cases, owing to paralysis of the bladder, the urine should be drawn with the catheter when six or eight hours have elapsed without urination.

THERAPEUTICS. — External Uses.—Belladonna liniment, plaster, and ointment are often employed to relieve pain, as local applications to painful areas. As the drug has to be used rather freely to get good results, some care is necessary to avoid general intoxication from absorption, especially in fair women and in children, owing to the thinness of their skin, or if the application is made where the skin is broken.

The plaster is very useful when applied over the seat of pain in **rheumatism**, especially **lumbago**, **neuralgia**, or when **abdominal pain** or **cardialgia** is only moderately severe. The ointment is also helpful when applied over chronically **inflamed joints**, oncoming **boils**, or other localized **inflammatory foci**. In painful **hemorrhoids** the following ointment is very helpful:—

℞ Cocaine hydro-
chloride gr. ij (0.13 Gm.).
Extract of bella-
donna leaves ... ʒj (4 Gm.).
Extract of hama-
melis ʒij (8 Gm.).
Petrolatum ʒj (31 Gm.).

Ointment to be applied locally.

In **anal fissure** the same ointment serves both to relieve pain and reduce spasm of the sphincter ani, a troublesome feature of these cases. The liniment or ointment of belladonna is very helpful when applied over **swollen lymphatic**, **parotid**, or other

glands. It relieves the pain in **sprains**. The application of a mild **sinapism**, to redden the skin slightly, will increase the efficiency of the belladonna. In **blepharospasm** the extract or ointment may be rubbed on to the eyelids externally.

When the mammary glands are swollen or tender, either early in lactation or later, when we wish to arrest **lactation** (on death or removal of infant or weaning), atropine [4 grains (0.26 Gm.) to 1 ounce (31 Gm.) of rose water] is a clean and efficient remedy to apply to the glands. The gland is first cleaned with soap and warm water, carefully dried, and the solution of atropine applied to the surface (avoiding the nipple and the areola) with a camel's hair brush and allowed to dry. The glands should then be drawn upward and inward (to take off weight and tension) and retained by means of a proper bandage. If preferred, the breast may be enveloped in lint wetted with the above solution. If the pupils dilate and the mouth becomes dry, the application should be removed.

In **ophthalmology** atropine is employed a great deal locally not only as a therapeutic agent, but as an important aid in diagnosis. A couple of drops of a 4 grain (0.26 Gm.) to the ounce (31 Gm.) solution of atropine dropped in the eye causes complete pupillary dilatation in about twenty minutes and complete loss of the power of accommodation in one and one-half hours. The effect on the pupil persists a number of days, while on the ciliary muscle it may even last two weeks. In many persons the atropine is absorbed sufficiently into the general system to

cause unpleasant dryness of the mouth, anorexia, *i.e.*, the full physiological effects of the drug. A much weaker solution will dilate the pupil than is required to paralyze the ciliary muscle.

Atropine dilates the pupil and renders accommodation impossible by paralyzing the ciliary muscles. Its use is justifiable in cases in which growths of the iris are to be attacked, or contraction of the ciliary muscle to be restrained, or investigation to be made concerning the conditions which obtain behind the iris. It is often used in cases in which not one of these three indications is present, and often to the misfortune of the patient. The accommodation often continues to be paralyzed long after the cause for producing it has been removed. Its use may result in an attack of glaucoma, an old solution may cause infection through slight defects in the conjunctival epithelium, repeated instillations may cause irritation of the connective tissue, and the diminution of the surface of the iris diminishes its power of absorption. Deutschmann (*Fortschritte der Med.*, April 1, 1906).

Atropine is preferable to homatropine, having many advantages over any other cycloplegic. It is reliable, allows more time, and enforces ciliary rest, though it is admitted that homatropine is more convenient, from the short duration of its effect, and is reliable in about 75 per cent. of cases. Gratiot (*Iowa Med. Jour.*, Nov., 1907).

The uses of atropine may be summarized as follows: 1. To dilate the pupil, in order to facilitate examination of the retina and lens (though for this purpose more rapidly acting mydriatics, such as homatropine, are preferable). 2. To paralyze accommodation, so that the refractive condition of the eye in its resting state can be ascertained and proper glasses

prescribed. 3. In certain inflammatory diseases of the eye to give it rest by paralyzing its muscles, to relieve local pain, or prevent blocking up of the pupil with pus and adhesions of the iris to the lens.

Mild solutions [1 or 2 grains (0.065 or 0.13 Gm.) to 1 ounce (31 Gm.)] instilled within the eyelids generally give prompt relief in all superficial inflammatory conditions of the eye in which pain, tenderness, and photophobia are present. In strumous **corneal ulcers** and **phlyctenular keratitis** (by diminishing photophobia and blepharospasm and lessening blood-supply) a few drops of a mild solution [1 grain (0.065 Gm.) to 1 ounce (31 Gm.)] two or three times daily will give relief. In **syphilitic iritis** where posterior or anterior synechiæ are a frequent complication, early and constant dilatation of the pupil should be secured through the use of solutions of atropine [2 to 4 grains (0.13 to 0.26 Gm.) to 1 ounce (31 Gm.)]. Atropine will relieve the **photophobia** of **acute conjunctivitis** and also that of **chronic conjunctivitis** associated with blepharitis and granular lids, if used in mild solution and not too frequently applied.

Internal Uses.—Disorders of the Respiratory Apparatus are often benefited by belladonna or atropine. In **acute coryza** with excessive flow of thin, watery secretion a small dose of atropine, $\frac{1}{200}$ grain (0.00033 Gm.), with monobromated camphor, 1 grain (0.065 Gm.) every two or three hours, is often efficient.

Atropine is able to abort a cold. The dose required ranges between 0.5 and 1.5 mg. ($\frac{1}{160}$ and $\frac{1}{60}$ gr.). This amount of atropine sulphate is dissolved in a glass of water and the

whole sipped in the course of an hour. By the end of an hour or two all symptoms have vanished. If they reappear the next day the dose is repeated. Kohnstamm (Therap. der Gegenwart, Bd. xlvii, Nu. 11, 1907).

In **hay fever** $\frac{1}{120}$ grain (0.0005 Gm.) of atropine three times a day until slight dryness of the mouth occurs is sometimes very efficient, especially if the fumes of epinephrin inhalant, 1:1000,—applied with an oil atomizer,—or epinephrin ointment are used at the same time.

In **pharyngitis** with increased secretion similar treatment is efficient; if there is much fever 1 drop (0.06 c.c.) of tincture of aconite with 2 drops (0.12 c.c.) of tincture of belladonna may be given every hour or two. **Aphonia**, due to fatigue of the vocal cords, may be removed very speedily by a morning and evening dose [$\frac{1}{120}$ to $\frac{1}{80}$ grain (0.0005 to 0.0008 Gm.)] of atropine; **hysterical aphonia** may not infrequently be quickly cured by means of the same treatment.

Diseases of Alimentary Tract.—

Various gastrointestinal disorders are benefited by belladonna. **Gastric hyperacidity**, when unrelieved by alkaline salts, magnesia, sodium bicarbonate, etc., usually yields when atropine, $\frac{1}{120}$ grain (0.0005 Gm.), is added to each dose of the latter. **Gastralgia** and the pain of **gastric ulcer** are also relieved by the use of atropine.

Good results are obtained by the use of atropine in the treatment of **gastric ulcer**. The subjective symptoms, especially pain, disappear quickly after beginning the treatment. Hyperacidity and hypersecretion are less quickly influenced. In the writer's cases pyloric stenosis due to cicatricial contraction was

either not at all or only slightly influenced. The writer agrees with the view of Eissinger and Hess that many ulcer cases are dependent upon an increased vagus tone. This increased vagus tone stimulates the gastric secretion as well as the gastric musculature, and can be diminished by a systematic use of atropine. Schick (Wiener klin. Woch., Bd. xxiii, S. 1229, 1910).

An old formula (Bartholow's) is very efficient in such cases:—

R *Atropine sulph.* ... gr. $\frac{1}{2}$ (0.013 Gm.).
Zinc sulph. gr. xxx (2 Gm.).
Distilled water ... ℥j (31 c.c.).—M.

From 3 to 5 drops twice or thrice a day.

In a study of the action of atropine in 28 cases of **gastric disorders** of various kinds, giving 0.001 Gm. ($\frac{1}{600}$ grain) hypodermically, once a day during 9 days, and in some cases 2 weeks. The writer found that it caused a decrease of gastric secretion, and of acidity, reducing pain and spasmodic contraction, the results corresponding with those of Riegel's experiments on animals. By reducing secretory activity it diminished acidity, thus arresting pylorospasm and pain. Pletneff (Med. Obozrenije, lxxix, No. 3, 1913).

The same combination is very effective in **pyrosis** and **chronic gastric catarrh**. **Vomiting of pregnancy**, **spasmodic vomiting**, or **spasm of the pylorus**, all due to excessive motor activity of the stomach and likewise persistent vomiting in **sea-sickness**, may all be relieved by the internal administration of $\frac{1}{120}$ grain (0.0005 Gm.) of atropine sulphate, in water, before meals; if the stomach rebels, the atropine may be given in suppository, or, dissolved in chloroform (1 to 96), it may be used on lint applied to the epigastrium. In **indigestion** with severe colicky pains, also in **mushroom** and **ptomaine poi-**

soning, belladonna or atropine affords marked relief.

Habitual constipation may be relieved by $\frac{1}{6}$ to $\frac{1}{2}$ grain (0.01 to 0.03 Gm.) of the extract in a pill, taken at bedtime.

Added to other purgatives it diminishes their griping action, and, since it increases peristalsis and allays spasm, it increases their efficiency. When there exists a torpor of the lower bowel aloin is a valuable addition. An excellent combination is

R. Aloin,
Ext. nux vomica,
Resin podophyllum,
 of each $\frac{1}{2}$ gr. (0.03 Gm.).
Ext. belladonna ... $\frac{1}{4}$ gr. (0.016 Gm.).

Make 2 pills; 1 or 2 at bedtime.

Pyrosis may be relieved by atropine ($\frac{1}{196}$ grain—0.00034 Gm.) combined with 5 drops (0.3 c.c.) of dilute muriatic acid, well diluted and taken before meals.

In **lead colic** belladonna, like opium, relieves constipation by removing the intense spasm of the intestinal muscles which causes it.

In **cholera infantum** atropine is sometimes efficient where other means fail. Bailey noted that infants bore atropine well, and gave almost adult doses to children only a few months old, combining the drug with relatively very small doses of morphine: for instance, $\frac{1}{80}$ grain (0.0008 Gm.) of morphine and $\frac{1}{150}$ grain (0.0004 Gm.) of atropine, repeated two, three, or four times in twenty-four hours, making the adult dose of atropine. This was found to control the phenomena of cholera infantum, which would have terminated life perhaps in a few hours without. Lauder Brunton also praises atropine in this disorder. In one of his cases for ex-

ample, in which a child was collapsed and apparently dying, a subcutaneous injection of atropine revived her for a time. This was followed by relapse; but another injection was administered, with good results, the child recovering.

Spasmodic Disorders.—These are favorably influenced by belladonna. It seems to enhance the analgesic action of the opiates in spasmodic neurosis attended by severe pain.

In pertussis it is considered one of the most reliable remedies. It is not adapted to all cases, but is most effective in the spasmodic stage and in those cases which are characterized by profuse bronchial secretion. One may employ an aqueous solution of atropine sulphate (1 to 480), giving 2 to 4 drops (0.12 to 0.24 c.c.) at a dose. The tincture of belladonna may be given in doses of from 3 to 5 minims (0.2 to 0.3 c.c.) every three or four hours, stopping when there is a perceptible dilatation of the pupils, or even slight reddening of the skin. The dryness of the throat and mouth may be relieved by small doses of the iodides, by small doses of wine of ipecac or antimonial wine, by occasional small doses of calomel, or by ammonium chloride. Westbrook suggests the following:—

R. Tinct. bella-
donna 3 to 5 mins. (0.2 to 0.3 c.c.).
Alum 1 dr. (4 Gm.).
Syrup of
Tolu 1 oz. (31 c.c.).
Water 2 oz. (62 c.c.).—M.

Of this mixture the child may be given a teaspoonful every two or three hours, day and night, if it is awake. When the spasm is marked and very frequent, the following is used:—

℞ *Tinct. bella-*
donna 3 mins. (0.2 c.c.).
Tinct. cam-
phorated
opium 2 to 4 drs. (8 to 16 c.c.).
Chloride of
ammonium. 1 dr. (4 Gm.).
Bromide of
ammonium. 2 drs. (8 Gm.).
Syrup of wild
cherry bark,
 enough to
 make 3 oz. (93 c.c.).—M.

Of this a teaspoonful, diluted, is given every two or three hours, night and day, if the child is awake. Forchheimer advocates the use of quinine in conjunction with belladonna.

Another spasmodic disorder in which belladonna, *i.e.*, atropine, has been found helpful is **tetanus**. It is given in small doses, preferably with morphine, at short intervals.

Two cases of **tetanus** in which atropine was employed. In the first case $\frac{1}{8}$ grain (0.008 Gm.) of morphine combined with $\frac{1}{300}$ grain (0.0002 Gm.) of atropine was given by the mouth every two hours for three doses and then every four hours. From the first dose the spasms markedly decreased in frequency and severity, and the patient was able to obtain good rest at night. In about four weeks the patient was up and about the house. In addition, small doses of calomel and sodium sulphate were given to keep the bowels open, and the wound was dressed with hot turpentine. The second case was a colored boy 3 years old showing well-marked trismus, though no wound could be found. He had stiffness of the muscles of the body. He was treated similarly, but with smaller doses, and by the beginning of the fourth week all symptoms had disappeared. This treatment was repeated in many cases of tetanus with the same result. Confirmatory of the use of atropine in tetanus is the fact that the govern-

ment veterinary surgeons employed large doses of belladonna with small doses of morphine in treatment of tetanus in animals, and that a fatal result rarely occurred. R. F. Secor (Lancet, May 21, 1910).

In asthma and in the dyspnea which accompanies **emphysema** belladonna gives great relief. During attacks of **asthma**, due largely to reflex spasm and narrowing of the bronchioles, atropine affords relief by paralyzing the motor endings of the vagus, relaxing spasm, and re-establishing thereby free respiration. In severe attacks atropine itself may be injected hypodermically in doses of $\frac{1}{120}$ to $\frac{1}{100}$ grain (0.0005 to 0.00065 Gm.) combined with $\frac{1}{4}$ grain (0.016 Gm.) morphine.

After the paroxysm is relieved, the effect may be prolonged by internal medication. Belladonna leaves may be used by the method of fumigation. The leaves previously dipped in a saturated solution of niter and then dried may be burned in a close apartment, or on a saucer, the fumes being inhaled from a paper funnel covering the same. Pastilles made of belladonna, stramonium, poppy, tobacco, etc., may be used. An excellent formula is Trousseau's for asthmatic cigarettes:—

℞ *Belladonna leaves*.. 5 grs. (0.3 Gm.).
Stramonium leaves,
Hyoscyamus leaves,
 of each 3 grs. (0.2 Gm.).
Extract of opium. $\frac{1}{2}$ gr. (0.013 Gm.).
Cherry-laurel water. q. s.

The leaves are moistened with a solution of the opium in the cherry-laurel water, and when dry made into a cigarette. Two to four such cigarettes may be smoked daily.

Belladonna is useful in the treatment of **spasmodic cough** and in spas-

modic croup, given between the paroxysms; more rapid measures are needed for the relief of the paroxysm itself. Atropine has also given good results in the initial stage of **influenza** to counteract the catarrhal phenomena of the upper respiratory tract, by restoring the circulatory equilibrium of the respiratory mucosa through its sympathetic supply.

In the treatment of **enuresis**, no single remedy has given such good and uniform results in suitable cases as belladonna. This distressing ailment may be caused by hyperacidity of the urine, relaxed condition of the sphincter vesicæ, or by an irritable condition of the vesical mucous membrane; belladonna gives prompt relief in the two last-named conditions. In male children **phimosis**, accompanied often by adhesion of the prepuce to the glans penis and retained smegma, is a frequent cause of enuresis; in these circumcision, and not belladonna, is indicated. Again, the presence of ascarides may be sufficient to cause nocturnal incontinence, especially in female infants and children; here again belladonna is of no avail. In suitable cases, as indicated above, atropine, in solution or in tablets, is best suited for internal administration. Beginning with a small dose at bedtime, the dose is gradually increased until systemic effects are produced. It must be remembered that as regards children generally too little of the drug is given. After the relief or cure of incontinence the best results are obtained by continuing the use of the drug for several weeks, in diminishing doses, with an occasional intermission of one to three days, during which time it is not given. This

advice holds good in treating spasmodic disorders generally.

In spasmodic conditions of the rectum or **rectal spasm** associated with **fissure, hemorrhoids, cancer, chronic constipation**, etc., a small suppository (6 to 10 grains—0.39 to 0.65 Gm.), containing from $\frac{1}{4}$ to $\frac{1}{2}$ grain (0.016 to 0.032 Gm.) of the extract, introduced well up into the rectum beyond the internal sphincter, gives great relief.

In **intestinal obstruction** or **volvulus** relief sometimes follows elevation of the pelvis on a firm pillow so as to allow gravity to act toward the thorax, especially when combined with starvation, and the use of belladonna and opium (Thomas Bryant). High enemas or bowel flushing enhance the chances of recovery (Stokes).

Nervous Disorders.—In **uterine pain** attended by hyperemia, spasm, or **dysmenorrhea**, a larger suppository (30 to 60 grains—1.94 to 3.88 Gm.), containing from $\frac{1}{2}$ to 1 grain (0.032 to 0.065 Gm.) of the solid extract, may be introduced high up within the vagina and retained by means of a tampon of non-absorbent cotton, at night. In **dysmenorrhea** the injection of atropine into the cervical canal has also been found helpful.

Report of several cases of **dysmenorrhea** in which injection into the cervical canal of 1 mg. ($\frac{1}{65}$ gr.) of atropine dissolved in 1 c.c. (15 minims) of water arrested at once the colic spasms in the uterus or prevented their development. If there is no speculum or syringe at hand the same effect can be realized by introducing a small cotton wad moistened with a 1 per cent. solution of atropine and pressing far back against the posterior vault of the vagina. This simple measure has proved effectual in

the writer's experience of fifteen years. Drenkahn (Zeit. f. Gyn., xxxiv, Nu. 47, S. 1529, 1911).

Atropine gives very satisfactory results in **neuralgia**, especially in neuralgia of the trigeminus, and in **sciatica**. In the former, a solution of the drug may be applied externally over the painful area, or instilled within the eyelids, or injected not subcutaneously, but deeply, into the tissues in the neighborhood of the affected nerve-trunk. In sciatica the last method is the best. The largest dose compatible with the safety of the patient must be used (generally $\frac{1}{100}$ to $\frac{1}{60}$ grain—0.00065 to 0.0011 Gm.), and decided curative results may be expected if the injection is made straight to the nerve by introducing the hypodermic needle perpendicularly through the overlying tissues. The ointment or plaster of belladonna is a useful application in **neuralgia** of various forms (mammary, intercostal, cervicodorsal, etc.). A few drops of aconite used to moisten the surface of a belladonna plaster before applying will in most cases increase its efficiency. **Earache**, when neuralgic in character and not produced by pressure of pus against the tympanum, may be relieved by instilling a few drops of a solution of atropine previously warmed. **Periuterine** and **dysmenorrheal neuralgias** are relieved by deep hypodermic injections of atropine in solution. **Muscular cramp** from injuries to the nerve-trunk are often relieved by atropine injected into the substance of the affected muscle. **Hepatic, intestinal, uterine, and renal colic** may be relieved by hypodermic injections of atropine, but the best results are reached when morphine and atropine are combined.

Vaginismus has been relieved by the topical use of pledgets of lint wet with a mild solution of atropine.

The **insomnia** of mental disorders and of **delirium tremens** may be overcome by the hypodermic injection of atropine when the following indications for its use are present: Coma vigil, great restlessness, weak heart, cold surface, cyanosis, clammy sweat. When there is a condition of hyperemia of the cerebrospinal centers (excitement with elevated pulse rate and increased arterial tension) atropine can only do harm.

Since atropine stimulates the heart and increases the blood-pressure, we find it useful in moderate doses in the collapse of fevers, **cholera**, **sunstroke**, and **cardiac syncope**. The dangerous **exhaustion consequent upon colliquative diarrhea** and **internal hemorrhage** indicate the use of atropine. In **congestive chill** due to **malaria**, atropine will sometimes save the patient after all other measures have failed.

In the **congestive chill** of malaria, especially when the skin is blue, cold, and moist, belladonna found very valuable. In a desperate case, having exhausted classic remedies, the writer dissolved $\frac{1}{4}$ grain (0.016 Gm.) of solid extract of belladonna in a few drops of water, and gave it hypodermically. Waiting an hour and seeing the patient no worse, he gave a second dose. In twenty minutes, the pulse and general conditions showing signs of improvement, he made ready and gave the third dose. Soon after this the patient became conscious, reacting nicely. Since that time the writer treated several cases, always with success, latterly substituting atropine sulphate for the belladonna. Having learned that the medicine does no harm, only good, he now begins more boldly, giving, at first, $\frac{1}{60}$ grain (0.001 Gm.) of atropine sulphate, and more in twenty or thirty

minutes if no very decided effects are produced. In some of his later cases the writer supplemented the atropine with a good dose of strychnine sulphate, say $\frac{1}{80}$ or $\frac{1}{20}$ grain (0.002 or 0.003 Gm.). I. L. Van Zandt (Texas State Jour. of Med., Jan., 1910).

It is also valuable for the prevention of **shock** during operative procedures with anesthesia. Atropine— $\frac{1}{75}$ to $\frac{1}{100}$ grain (0.00085 to 0.00065 Gm.) given before the administration of ether—reduces the chances of shock. By promoting contraction of the arteries, it antagonizes the dangerous fall of blood-pressure produced by chloroform. It may be used by intravascular, hypodermic, or intravenous injection.

While the atropine reaction in cases of **bradycardia** cannot be relied on absolutely, yet it furnishes valuable presumptive evidence, and as it is so harmless and within the reach of every practitioner it deserves wider application. It is invariably positive in the cases of bradycardia of nervous-cerebral origin, and negative with bradycardia from heart-block. The test is merely the hypodermic injection of 0.002 Gm. ($\frac{1}{32}$ grain) of atropine sulphate and control of the heart-beat afterward. The heart-beat is not modified by the drug in case of actual heart disease, while the pulse is accelerated when the myocardium is sound. The reaction becomes evident in 15 minutes, and reaches its maximum in about an hour. Roch and Cottin (Semaine méd., Oct. 30, 1912).

Hemorrhagic Disorders.—Atropine has been highly recommended in many disorders characterized by an undue flow of blood. In **metrorrhagia** $\frac{1}{120}$ grain (0.0005 Gm.) twice daily with tamponing is very efficient. In **menorrhagia**, **post-partum hemorrhage**, and **hematemesis** in tuberculosis, the same dose, given hypo-

dermically, but at shorter intervals, has also given excellent results.

After studying the reports of many physicians with reference to the clinical results, the writer concludes that atropine is of considerable value in hemorrhage. In full doses it has been successful in controlling **menorrhagia**, **metrorrhagia**, **post-partum hemorrhage**, **hemophilia**, **intestinal hemorrhage**, **hemorrhage following abortion**, and **hematemesis**. By stimulation of the vasodilators blood would be drawn into the capillaries and emptied out of the veins. W. F. Waugh (Med. Record, Nov. 27, 1909).

The **night-sweats** of phthisis may be checked by the subcutaneous injection of atropine; $\frac{1}{60}$ grain (0.0011 Gm.) at bedtime is usually required. The copious perspiration induced by drugs such as pilocarpine, opium, alcohol, and other diaphoretics, may be checked by the use of atropine.

Belladonna is useful in cutaneous neuroses, **prurigo**, **herpes zoster**, **erythema**, and **eczema**. Sufficiently large doses to maintain a mild physiological action must be used. **Hyperidrosis** and unilateral **sweating** are arrested by the internal or by the local application of the belladonna preparations. According to Liégeois, extract of belladonna in doses of from $\frac{2}{13}$ to $\frac{1}{3}$ grain (0.01 to 0.021 Gm.) is the best remedy in chronic **urticaria**, which appears to be due to an acute edema of the connective tissue of the skin as the result of active vasomotor dilatation. For the pruritus of **lichen**, Brocq gives fractional doses of tincture of belladonna: 1 to 4 drops *t. i. d.*

Atropine in solution (4 grains to 1 ounce—0.26 to 31 Gm.) may be applied externally in all painful and congested conditions of the skin. **Erythematous dermatitis**, **erysipelas simplex**, **pruritus of the vulva**, and **fi-**

sure, etc., may be relieved in this way. The pain of **cancerous infiltrations** of the skin may be relieved by painting the surface with an atropine solution, and, when the skin has become disintegrated through sloughing, lint dipped in a weak solution of atropine and applied to the surface gives relief. The troublesome **pruritus of icterus** or **diabetes** is best dealt with by calmative applications such as a flannel compress saturated with a solution of atropine, 1 to 500, covered with a sheet of oiled silk. (Besnier.)

Antidotal Uses.—In **opium poisoning** atropine is useful in doses sufficient to stimulate the circulation and respiration, whereby the secretion of urine is increased and the elimination of the poison hastened. For this purpose $\frac{1}{80}$ to $\frac{1}{60}$ grain (0.0008 to 0.001 Gm.) may be given hypodermically every hour or two, according to the gravity of the symptoms and the response of the nervous system to the remedy. The same remarks apply to the treatment of **poisoning by calabar bean** (**physostigmine, eserine**), for which atropine is a more decided antidote. The **tinnitus** due to **quinine** is considerably diminished by adding enough atropine to each dose of quinine to aggregate per day not more than $\frac{1}{120}$ grain (0.0005 Gm.). It has likewise been found to diminish the secretion of bronchial mucus during **ether anesthesia**.

A suggestive action of atropine is its prophylactic power against horse-serum **anaphylaxis**, clearly demonstrated experimentally.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

BENZOIN; BENZOIC ACID AND THE BENZOATES.

—Benzoin is a balsamic resin or gum, the concrete juice of the *Styrax benzoin*, a large tree, native of Peru. It occurs in the form of agglutinated lumps or tears, yellowish brown in color, with a milk-white interior. Benzoin has an agreeable balsamic odor, and a slight aromatic taste. It is easily pulverized, the process being apt to excite sneezing. It is almost wholly soluble in 5 parts of moderately warm alcohol and in solutions of the fixed alkalies. Its chief constituents are resin and a volatile oil, *benzoic acid* (14 to 20 per cent.), and a small proportion of *cinnamic acid*. Benzoin also contains a principle termed *styracin* (2 to 3 per cent.), and also, in smaller quantities, *vanillin*, *styrol*, and *benzaldehyde* and, in large bulk (75 per cent.), the cinnamic esters of *benzorcsinol* and *resinotannol*.

Benzoic acid is the most important of the above series, because it forms very soluble and neutral salts, the *benzoates*, with alkalies. It is obtained in various ways: from various benzoin, Asiatic and American; from hippuric acid derived in turn from the urine of horses and cattle; from the oxidation of toluene with nitric acid, etc. The best acid is obtained, however, from Siamese benzoin. It should always, as directed by the U. S. P., give off the aromatic odor of benzoin.

PREPARATIONS AND DOSES.

—Owing to its property of preventing rancidity, benzoin is added to ointments, forming the benzoinated lard, or *adeps benzoïnatus*—2 per cent.

The tincture of benzoin, or *tinctura benzoini*, may be given in 30-minim

(2 Gm.) doses. It is also used as an inhalant, 1 or 2 teaspoonfuls being dropped in $\frac{1}{2}$ pint of hot water, the steam of which is inhaled through a cone made of a folded towel. Another preparation extensively used in the latter way is:—

The compound tincture of benzoïn, the *tinctura benzoini composita* [which contains benzoïn, 10 Gm. ($2\frac{1}{2}$ drams); aloes, 2 Gm. (30 grs.); storax, 8 Gm. (2 drams); tolu, 4 Gm. (1 dram); alcohol, q. s. ad 100 c.c. ($3\frac{1}{3}$ ounces)], is used extensively for inhaling purposes in the manner described above, but has also been given internally. Dose, 30 minims to 2 drams (2 to 7.5 c.c.).

Benzoic acid, or *acidum benzoicum*, which occurs in white, pearly plates or needles that become yellowish with age, has an agreeable aromatic odor, but a somewhat pungent taste. It is soluble in 1 to 280 parts of cold water, 1 to 15 of boiling water, 1 to 10 of glycerin, and 1 to 2 of alcohol. Its solubility in water is increased by sodium borate. Dose, 5 to 15 grains (0.33 to 1 Gm.). It should not be administered in capsules or cachets, owing to its irritating action on the gastrointestinal mucosa.

Of the many salts of benzoic acid that have been introduced, three are official.

The sodium benzoate, or *sodii benzoas*, which occurs in the form of a white powder or crystals having a sweetish taste and soluble in 1.6 parts of water and in 43 parts of alcohol. Dose, 5 to 30 grains (0.33 to 2.0 Gm.).

The ammonium benzoate, or *ammonii benzoas*, which occurs as a white powder or crystals having a saline, bitter, and acrid taste, soluble in 10.5 parts of water and in 25 parts of

alcohol. Dose, 10 to 30 grains (0.66 to 2.0 Gm.).

Both the above salts in solution should be kept in well-stoppered bottles.

The lithium benzoate, or *lithii benzoas*, a light, shining, white powder or crystals having a fresh, sweetish taste, soluble in 3 parts of water and 13 parts of alcohol. Dose, 10 to 30 grains (0.66 to 2.0 Gm.).

Benzoic acid lozenges, or *trochisci acidi benzoici*, containing $\frac{1}{2}$ grain (0.03 Gm.) of benzoic acid each, with a fruit base, are official in the British Pharmacopœia.

PHYSIOLOGICAL ACTION.—

Probably the main property of benzoïn as represented by benzoic acid is its antiseptic power. According to Pouchet, this is superior to that of salicylic acid, and even of phenol or carbolic acid, when the benzoic acid employed is free or in solution. A 1:1000 solution suffices to antagonize very actively the pullulation of atmospheric bacteria; while a solution of 2:1000 approximating saturation will sterilize a culture medium; to inhibit cultures in actual development, however, a 20:1000 solution is necessary. The sodium benzoate owes its value to the same property, owing to the fact that it is broken up when absorbed, liberating the benzoic acid. The latter is eliminated as hippuric acid, formed in the kidneys.

When brought into contact with the buccal mucosa, benzoic acid strongly excites it; powdered, it also excites the nasal, conjunctival, buccal, etc., acini, producing hypersecretion. It is probably to the combination of its antiseptic and stimulating actions that benzoic acid, or the preparations in which it enters, owes its

therapeutic properties when used locally.

When administered internally, sodium benzoate exerts, besides the antiseptic action above mentioned, the power of enhancing the elimination of waste products through the renal system. Moreover, in keeping with salicylic acid, it increases biliary secretion—an effect it has, in fact, on all secretions, including that of the bronchi. Hence the great value of benzoïn and its preparations in the acute diseases of the respiratory tract.

On the heart and circulation, benzoic acid acts much as does salicylic acid, producing, but only in excessive doses, cardiac acceleration, then slowing with lowering of the temperature. All these are toxic phenomena, however, benzoic acid being endowed therapeutically with no antipyretic property.

POISONING BY BENZOIN PREPARATIONS.—A toxic dose of benzoic acid causes vomiting, headache, tinnitus, a sensation of heat in the abdomen, increased frequency followed by slowing of the pulse, diaphoresis, and a marked increase of the bronchial secretion. In animals it causes death by producing bulbomedullary paralysis with respiratory arrest. Man is more susceptible than warm-blooded animals to its toxic effects. Irritation of the gastrointestinal mucosa is very marked, vomiting being sometimes accompanied by gastric hemorrhage. The main action of the toxic dose seems to be spent in the stomach and duodenum, there being no diarrhea. A single dose of 75 grains (5 Gm.) of sodium benzoate has sufficed to cause nausea and vomiting. Marked sweat-

ing, salivation, an abundant expectoration of mucus, and hematemesis have also been observed after large doses (Pouchet).

Schreiber took in two days about $\frac{1}{2}$ ounce (15 Gm.) of the acid, and experienced only a feeling of abdominal warmth, spreading over the whole body, accompanied by an increase of the pulse rate amounting to 30 beats per minute; also increased excretion of phlegm, with slight disturbances of digestion.

Rarely a patient is encountered in whom the preparations of benzoïn, owing to an idiosyncrasy, produce an eruption, erythema, or even urticaria. These readily pass off, especially if **saline solution enteroclysis** is resorted to to increase the osmotic properties of the blood.

THERAPEUTICS.—Disorders of the Respiratory Tract.—It is in this class of disorders that the preparations of benzoïn have proven most efficient. When employed early in **acute coryza** sodium benzoate in 10-grain (0.66 Gm.) doses every three hours in a glassful of water, first gargling, then swallowing, often suffices to abort the cold. This treatment is equally valuable in the incipient stages of **tracheobronchitis**, **pharyngitis**, and **laryngitis**, modifying favorably the pain, dysphagia, and inflammation in a short time. Boislinière observed that when 4 to 15 grains (0.25 to 1 Gm.) were given every one or two hours in **follicular tonsillitis** the disorder lasted but twelve to thirty-six hours instead of several days. It is an excellent agent for the various disorders of the singing voice. In **tonsillitis**, as well as in **acute laryngitis**, rapid results are attained by the use of inhalations of the steam of a pint of hot water containing 2

drams (7.5 c.c.) of the tincture of benzoin, provided the patient is given at the same time 5 grains (0.33 Gm.) of the benzoate of sodium every two hours. The hot solution of benzoin is placed in a previously warmed vessel, and, the latter being covered with a towel folded into a cone, the patient inhales through the upper opening of the latter. In **senile bronchorrhea** ammonium benzoate reduces the sputum and counteracts its fetid odor. Benzoic acid lozenges containing $\frac{1}{2}$ grain (0.033 Gm.) of benzoic acid each, with a fruit base, are excellent for any of the above disorders.

Disorders of the Urinary Tract.—Owing to the antiseptic and stimulating properties of benzoin, its preparations have been considerably used in this class of cases, especially where the bladder and urethra are involved. Benzoic acid is of especial value in **chronic cystitis** with fermentation; it counteracts the ammoniacal condition of the urine and the irritation and tenesmus, and also the unpleasant odor. It is said also to promote the solution of **gravel** or **ureteral calculi** of whatever nature, and should be given with considerable water. The sodium benzoate has given good results in **urethral irritation**, and even in **gonorrhea**, affording an excellent adjunct to the local measures employed. In **chronic gout** the lithium benzoate has been found of considerable value, owing to its power to promote the elimination of intermediate products of metabolism, uric acid, etc. Benzoic acid is also useful in some forms of **enuresis** in children in 3- to 5- grain (0.2 to 0.33 Gm.) doses.

Disorders of the Skin.—The tincture of benzoin is exceedingly valu-

able as a local application for **abrasions, cuts, frost-bite, bruises, scratches, chapped hands and lips, and fissures**. It is not only antiseptic, but protective, sealing the wound and preventing infection. It does not irritate, as does iodine, nor does it expose the tissues to necrosis, a marked defect of phenol. Even in **wounds** of a more severe type tincture of benzoin may be employed as a dressing after thoroughly cleansing the lesion and the surrounding tissues. In **anal fissure** it is markedly effective used in the same manner. **Fissured nipples** are equally benefited, the protective covering the tincture affords aiding materially in the healing process.

The tincture serves as a very useful dressing in **foul ulcers** after careful cleansing of the latter with an antiseptic solution and drying. The tincture of benzoin, 2 drams (8 c.c.); glycerin, 2 drams (8 c.c.), and rose water, 4 ounces (120 c.c.), applied as a lotion to **eczema, pityriasis, urticaria**, and **scabies** proves efficient in most cases, relieving also the itching.

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

BENZYL BENZOATE.—Benzyl benzoate is an antispasmodic isolated in 1919 by D. I. Macht. It is a benzyl ester found in some of the balsamic resins, balsam of Peru, cinnamein, tolu, etc., either alone or in combination, and also in the volatile oils of many fragrant flowers, tuberose, gardenia, hyacinth, jasmin, etc. A systematic examination of the opium alkaloids showed that they could be divided into 2 general classes: 1, the pyridin phenanthrene group, to which morphine belongs, was found to *stimulate* contractions of unstriated muscular fibers;

and 2, the benzyl isoquinolin group, to which papaverin belongs, tended to *inhibit* the contractions of the same fibers. This antagonism suggested that simpler non-narcotic compounds might likewise inhibit unstriated muscles. This led to the discovery that benzyl benzoate and benzyl acetate, as does papaverin, possess this property. Hence the antispasmodic effects found to be produced in ureteral colic and excessive intestinal peristalsis.

ADMINISTRATION.—Benzyl benzoate is a colorless, oily liquid with a faint aromatic odor, but a bitter, burning taste, which is lasting. It may be given by the mouth in a 20 per cent. alcoholic solution, 15 to 25 drops in cold water being given 3 or 4 times a day for adults. Though practically non-toxic, larger doses are unnecessary. For infants and children the dose is reduced proportionately. An aromatized suspension is available in the shops, the strength of which is 20 per cent., thus requiring 5 times the above dosage to obtain corresponding effects.

It is now available commercially in soluble gelatin globules, each containing 5 minims (0.3 c.c.), which are termed "benzylets."

Benzyl benzoate may also be administered hypodermically, a 20 per cent. solution in oil being available. The dose ranges from 10 to 60 minims (0.6 to 3.6 c.c.).

Hirschfelder (Minn. Med., Aug., 1920), to avoid the unpleasant taste, gives pure benzyl benzoate, 10 parts; emulsion of acacia, 5 parts; elixir eriodictyi aromaticum (N. F.), 35 parts; dose, 1 teaspoonful. The relief occurs within one-half hour after taking and is lasting.

PHYSIOLOGICAL ACTION.—Jackson, Nielsen and Higgins (Jour. Lab. and Clin. Med., Apr., 1921) obtained marked intestinal relaxation with injections of relatively small amounts of benzyl benzoate and benzyl cinnamate. After repeated injections of large doses of benzyl esters into the blood stream, the arterial blood became very venous in appearance. The coagulation time of this blood was not affected.

UNTOWARD EFFECTS.—Heller and Steinfeld (N. Y. Med. Jour., July 31, 1920)

found that (1) benzyl benzoate has no toxic effects upon the leucocytes of rabbits; (2) controls of benzol showed the well-known depression of the leucocyte count; (3) a wide margin of safety is present between the therapeutic doses and the toxic doses of benzyl benzoate, based upon observations on rabbits.

THERAPEUTICS.—The clinical disorders in which Macht found benzyl benzoate of service were the following: **Excessive peristalsis**, as in **diarrhea** and **dysentery**; **intestinal colic** and **enterospasm**, including the post-operative form; **pylorospasm**, functional, reflex or due to ulcers or tumors; **spastic constipation**; **biliary colic**; **ureteral or renal colic**, **vesical spasm**, **spasmodic pains due to contractions of the seminal vesicles**, **uterine colic** which had resisted pessaries, curettage, and other measures; **arterial spasm with hypertension or high pressure**, the effects being more lasting than the nitrites, and in some cases more efficient; **bronchial spasm in true asthma**, the latter test having been based upon 200 cases.

J. C. Litzenberg (Jour. Amer. Med. Assoc., Aug. 23, 1919) obtained good results in **dysmenorrhea** and urges a trial of benzyl benzoate before dilatation or other pelvic procedures are resorted to.

Musser (N. Y. Med. Jour., Oct. 16, 1920) used benzyl benzoate in 6 cases of **hypertension**, plus a few simple general hygienic directions. In no case did he see any effect, confirming the observations of several colleagues. He also tried it in 2 cases of **angina pectoris**. In several other **painful or disagreeable spastic conditions** its action was highly beneficial.

J. Ruhräh (Amer. Jour. Med. Sci., Jan., 1921) has used benzyl benzoate sufficiently to be able to recommend it in **bronchial asthma**, **spasmodic bronchitis**, **gastric or intestinal colic**, **hiccough**, and **spasmodic constipation**. It has been recommended by others in **excessive peristalsis**. In **whooping cough** its action is often most beneficial, but the results are uncertain, as is the case with all other antispasmodics in this disease. In general **convulsive conditions** not dependent on organic lesions of the central nervous system, especially in the **new-born**, the drug will be found of benefit.

BENZOSULPHINIDUM. See SACCHARIN.

BERIBERI.—This term, commonly used for tropical endemic multiple neuritis, is the Cingalese name of the disease, derived by intensive reduplication from “beri” = weakness. The Japanese call it *kakke*.

DEFINITION.—An endoepidemic disease or group of diseases, due in most instances to the excessive consumption of polished white rice, *i.e.*, rice deprived of its pericarp in the process of milling, occurring chiefly in tropical and subtropical countries, characterized by multiple peripheral neuritis, associated in many instances with edema, cardiac weakness, respiratory irregularities, malaise, gastrointestinal disorders, and fever, sometimes terminating in death.

SYMPTOMS.—The ever-present and essential feature of this disease is the multiple neuritis, usually of rapid development, and characterized by pain, tenderness, disorder of the tactile sense, abolition of the tendon reflexes, loss of muscular tone, muscular weakness amounting in some instances to complete paralysis, and, at a later period, muscular atrophy. Preceding and accompanying these nervous symptoms, there may be some dyscrasic, scurvy-like state of malnutrition, some form of acute or chronic toxemia, or, most frequently, the clinical symptoms of acute bacterial or plasmodial disease—rise of temperature, headache, furred tongue, anorexia, gastrointestinal disturbance, etc.

In cases in which the phrenic and pneumogastric nerves become involved in the neuritic process, respiratory weakness, rapid pulse, heart

failure, edema, and anasarca are shown.

Two clinical varieties of the disease are described: the “wet” and the “dry,” that is, with edema and without.

In “wet” beriberi the edema appears early and constitutes the characteristic differential symptom. A boggy swelling is noticed first in the lower extremities, increases steadily in amount and in extent, frequently developing into a general anasarca. The skin becomes pale, watery, and bloodless, the subcutaneous areolar tissue waterlogged, and effusions into serous cavities occur. The respiration is embarrassed, the heart action weak and rapid, arterial tension is low, the carotids pulsate violently, and there is often great precordial distress. A fatal termination within a few days after the first appearance of the disease is not infrequent (“pernicious beriberi”).

The sensory, motor, and reflex symptoms of peripheral neuritis may be elicited by examination, but are often inconspicuous in wet beriberi, being masked or overshadowed by the distressing cardiac weakness and anasarca.

Fever, nausea, coated tongue, albuminous urine, intestinal disorder, and other general constitutional symptoms are often present. The onset sometimes occurs with a chill or rigor. Vomiting of blood has been noted.

In favorable cases there is gradual subsidence of the anasarca, disappearance of the heart irregularity and weakness, and of the sensory neuritic symptoms, leaving the patient with some degree of muscular atrophy and paralysis; this latter also slowly sub-

sides, and entire recovery supervenes after weeks or months.

In "dry" beriberi the peripheral neuritic disturbances are more in evidence and the anasarca and cardiac weakness absent. The onset is less acute, the course less rapid, the mortality less.

Pain in the extremities is a prominent and often distressing feature. It may be neuralgic in character, or boring, stinging, burning, and accompanied by formication and by trophic changes in the skin. Tactile anesthesia and other sensory defects are occasionally present. Cramps are sometimes complained of. Tenderness on pressure is usual.

Muscular tonus is lost, muscular weakness or even total paralysis common, the knee-jerks absent, the gait shuffling and unsteady, foot-drop conspicuous.

Muscular atrophy supervenes and may reach an extreme degree in the severer minority of cases, resulting in long-continued paralysis, or even permanent contracture and laming. Trophic joint deformities also occur.

In these "dry" cases, there is often an accompanying dyscrasic state, evidences of malnutrition and toxemia, and disturbance of the stomach. Fever is sometimes shown; malaise and emaciation more frequent.

The course of this form of beriberi extends over weeks in mild forms; months or a year or more in the severe ones.

In both varieties of beriberi, as in other forms of neuritis, the distribution, extent, severity, duration, and clinical course vary widely at different times and places and in different cases.

The lower extremities are usually

first and most affected, although in many instances the nerves of the upper extremities become conspicuously involved. In many instances practically all of the spinal and many of the cranial nerves are attacked. Rarely the arms are more involved than the legs.

The associated general constitutional symptoms likewise vary much in character and severity, being sometimes so slight as to be overlooked, at other times greatly predominating over the symptoms of neuritis.

DIAGNOSIS.—The recognition of this disease is easy if it be borne in mind that the characteristic symptoms are those of multiple neuritis, as above outlined.

If there is pain, tenderness and other sensory disturbances, muscular weakness, loss of muscular tone, muscular atrophy, and absence of the deep reflexes, there is neuritis. If this neuritis is occurring among a number of persons about the same time and place it is properly described as "endemic neuritis," and if endemic multiple occurs in warm countries, in camps, in hospitals, or on shipboard it is called "beriberi."

The chief opportunity for the exercise of diagnostic skill is in discovering the cause or causes to which the multiple neuritis is due.

As stated in the definition, beriberi has been found to be due to the use of polished rice. This view has replaced a collection of theories which may, indeed, be characterized as very numerous. A few of these will suffice to illustrate this fact.

ETIOLOGY.—The majority of medical men who were brought in contact with endemic neuritis in the tropics became convinced that the

disease was primarily bacterial or plasmodial in origin, and much effort was expended by many competent and trained investigators in the attempt to isolate a specific micro-organism—always without success.

Remembering that beriberi is essentially a polyneuritis, and how many different factors caused polyneuritis in temperate climates, *i.e.*, alcohol, arsenic, lead, mercury, phosphorus, syphilis, malaria, and practically all of the infectious fevers, as well as wetting and chilling of the surface of the body, insufficient or improper food, etc.; and, remembering, also, that these factors would also produce polyneuritis in warm countries and on ships sailing from tropical ports; it seemed quite unreasonable to expect the discovery of a *specific* microbic cause, that is, an organism always causing beriberi, never causing anything else, and without infection by which organism beriberi cannot occur.

The most which we could expect was the eventual discovery of one or possibly more bacterial or, more likely, plasmodial organisms causing malaria-like disease and producing in some instances a secondary or complicating multiple neuritis. It seems, therefore, prior to the unmilled rice phase of the question that the following were the main causes of beriberi.

1. Micro-organismic diseases of any kind. Of the known pathogenic organisms, the malarial plasmodium is the most frequent factor in the production of endemic multiple neuritis. Some as yet unknown related form of pathogenic micro-organism may be discovered the poison of which may more often cause peripheral neuritis.

2. Malnutrition from insufficient or improper food.

Report of experimental work showing that beriberi cannot be ascribed to decorticated rice alone, as similar hulling of all other grains and legumes is liable to bring on the symptoms of beriberi. Even sterilization of the unhulled grains may bring on the same set of symptoms. The nervous manifestations from these deficiency disturbances open a new chapter of pathogenic neurology. "Life is necessary to life," and a rational diet should include the digestible maximum of fresh, "living" foods. The use of ultra refined flour, of sterilized meats, vegetables, milk, etc., kept up too long and too systematically, may be responsible for various deficiency disturbances. Weill and Mouriquand (*Revue de Méd.*, Paris, xxxv, No. 2, 1917).

3. Exposure to dampness and cold, wetting of body surface and subsequent chilling: wading or standing in water, etc.

4. Unhygienic or unfavorable surroundings of any kind, bad ventilation, overcrowding, etc., or anything tending to lower vitality or power of resistance.

5. Use of alcohol.

Any one of the above may cause a multiple neuritis. The first, second, and third, alone or in combination, are most important in causing the endemic form. To them also was attributed that form of multiple neuritis known as beriberi or kakke. All these causes were, however, found to play a secondary rôle, if any, in the genesis of the disease.

Fowls fed on undermilled rice combined with large amounts of sodium chloride are not attacked by multiple neuritis. In fowls from which all food is withheld, and only water allowed, multiple neuritis develops. Fowls starved on reduced amounts

of a neuritis-preventing undermilled rice acquire multiple neuritis. Fowls kept entirely without food and those which are given all they will eat of polished rice lose weight with almost equal rapidity in the great majority of cases. A loss of at least 21 per cent. of the body weight almost invariably occurs before any signs of multiple neuritis become apparent. The signs, symptoms, and nerve appearances are identical in neuritis produced by inanition and in that caused by feeding polished rice. Spasticity is a late development in some fowls in which neuritis develops; they are then saved from death by the institution of mixed feeding. In neuritis-producing rice and in beriberi-producing dietaries both the phosphorus and the potassium are markedly reduced in amount, the latter in greater degree than the former. Chamberlain, Bloombergh, and Kilbourne (Military Surgeon, Aug., 1911).

The polished rice theory is not of a recent discovery, as generally believed. As stated in a study of the question by Chamberlain, Bloombergh, and Kilbourne, of the Medical Corps of the United States Army (Military Surgeon, Aug., 1911), as far back as 1896 Eykman (Polyneuritis bij. Hoenders, etc., 1896), a Dutch physician, conducted feeding experiments with fowls and found that they would develop polyneuritis when fed on polished rice, but would not do so when given either padi (unhusked rice) or red rice. These experiments were repeated and verified later by Grijns (Med. Lab. Anal., etc., Weltevreden, 1900), Sakaki (Sei-i-Kwai, Mar. 31, 1903), and others, and it was shown that the presence of a part of the pericarp or the addition of rice polishings would likewise prevent the disease in fowls. Polyneuritis of fowls was then thought, and still is thought by many,

to be analogous to beriberi of man, and, since the fowl is easily experimented with, and is one of the very few animals thus affected, it became the favorite subject for feeding experiments in connection with beriberi. There has, however, always been in the minds of many a doubt whether these two diseases are truly analogous, and some have felt that experiments on man, or on an animal more closely related to man than the fowl, were necessary if we are to learn much more about the etiology of beriberi.

Vordeman ("Onderzoek naar het verband tusschen den aard der rijstroeding, in de gevangenissen of Java en moedoera en het voorkomen van beriberi onder de geïnternerden," Batavia, 1897), in 1895-1896, in the prisons of Java fed polished and undermilled rice to different groups of men and succeeded in greatly reducing the number of cases of beriberi by the use of the latter variety, and he urged the substitution of red (undermilled) for white (polished) rice in the public institutions of Java.

Braddon ("Cause and Prevention of Beriberi," London, 1907) gave many additional instances of the ill effects of polished rice and beriberi-preventing qualities of the parboiled or "cured" rice, but thought the former carried a toxin generated in it after milling. Others, having in mind the evidence furnished by previous experiments and epidemics, felt that a privation theory would best account for the occurrence and distribution of beriberi, and experiments were conducted with prisoners, laborers, etc., to prove or disprove the correctness of their deductions.

It remained for Fraser and Stanton (Lancet, Feb. 13, 1909) to prove beyond all reasonable doubt, in a series of experiments on laborers in the Malay peninsula, that beriberi could be absolutely prevented by feeding "cured" (parboiled) rice, and that it would occur in the same places and under the same conditions when the men were given polished rice. Since these experiments, it has been shown in many countries that the feeding of undermilled rice (which had not been parboiled) has the same beriberi-preventing influence as the use of parboiled rice, and that the beneficial effects of cured rice are due to the adherent pericarp and aleurone layer, and not directly to the process of "curing."

During 5 years in a wheat-eating country where beriberi is fairly common (Newfoundland and Labrador), the writer found that when from any cause the people have been on a diet of overmilled wheat (ordinary fine white wheat flour), beriberi developed. Little (Jour. Amer. Med. Assoc., June 29, 1912).

For some years a disease similar to the description of tropical beriberi has been endemic in Newfoundland, according to the writer. During the last 4 years the number of cases occurring annually has been decidedly on the increase. This disease is confined chiefly to the outposts, and is not solely an affliction of the poorer class. Osler speaks of beriberi among the fishermen on the Grand Banks, but about all the cases here are among the shoremen, that is, men fishing 2 or 3 miles from land in small boats. Gilbert Parker (N. Y. Med. Jour., Aug. 15, 1914).

Whether the disease is a purely nutritional one dependent upon the absence of phosphorus-containing vitamins in spoiled or highly polished rice, or whether it is due to an infection against which the vitamins act as specific antidotes are not de-

termined. One of the proximate principles of this substance has been isolated by Young, and is variously known as Young's basic substance or "beriberi vitamins." The researches of the authors seem to indicate that this basic vitamin has a specific action in preventing the development of the paralytic symptoms of "dry beriberi," whereas another substance in the pericarpal layers of the rice grain is specific against the edema and heart-failure arising in connection with "wet beriberi." Vedder and Williams (Philippine Jour. of Sci., June, 1913).

The chemistry of rice polishings was studied by the writers. They failed, however, to isolate the curative substance which occurs in rice polishings. It is apparently decomposed during the fractionation, and all trace of it is lost. The existence of "vitamine" in the sense that Funk employed that word is therefore disproved. Fraser and Stanton (Lancet, May 15, 1915).

The writer observed a case of relapsing beriberi in a soldier, about 28 years old, contracted in India. His diet was the regulation army fare—meat, vegetables, milk, bread and butter, tea, and occasionally a bit of rice or sago pudding, but at no time in his life was he ever on an exclusive or continuous rice diet. This rather opposes the accepted view that beriberi is due to lack of vitamins produced through the consumption of quantities of polished rice. J. C. McWalter (Brit. Med. Jour., Feb. 5, 1916).

The identity of the substance or substances which are removed by destroying the pericarp of the grain has not as yet been determined.

All recent experimental work, both in man and poultry, has shown that there are 2 factors in the production of beriberi: (1) the absence of an accessory food factor or vitamin; (2) the use of certain foods which are the direct and immediate cause of the disease. Carbohydrates ap-

parently constitute this second factor. It seems probable that in the absence of their specific vitamine they undergo an aberrant hydrolysis with the production of toxic by-products, or end-products, thus producing beriberi. The striking symptoms of beriberi and the widespread visceral and nervous changes seen post mortem cannot be accounted for by the hypothesis of a slowly progressive diffuse degeneration of the nervous system. Until the physical chemistry of the vitamins and the metabolism in beriberi—both totally unexplored fields—have been more fully investigated, the pathogenesis of beriberi will remain in part obscure. Walshe (*Quarterly Jour. of Med.*, July, 1918).

PATHOLOGY.—The essential pathological change is parenchymatous degeneration in the nerve filaments of the affected peripheral nerves and atrophy of the muscles to which the motor fibers of these nerves are distributed. In those cases resulting fatally from heart-failure, it is usual to find the heart wall soft, pale, flabby, and degenerated. In the "wet" cases, general edematous infiltration of areolar tissue and effusion into pericardial, pleural, and peritoneal cavities are found.

Other less characteristic morbid changes are met with, dependent upon the nature and severity of the dyscrasic, toxic, or acute germ disease factor which causes or accompanies the neuritis. Gastritis and enteritis with hemorrhage have been seen. Hepatic congestion, parenchymatous hepatitis, acute nephritis, congestion and edema of the lungs, enlargement of the spleen, etc., have been described.

Referring to the pathological affinities between beriberi and scurvy, the writer noted a striking eccentric

hypertrophy and dilatation of the right heart, with extensive fatty degeneration of the same musculature (the left heart remaining normal), and the severe degeneration of the vagus nerve observed in several fatal cases of scurvy from the Rand, furnish new and additional facts which show the intimate relationship, as to etiology, between the 2 diseases. S. T. Darling (*Jour. Amer. Med. Assoc.*, Oct. 10, 1914).

The pathologic findings are less pronounced in the peripheral nerves in acute than in chronic beriberi, but the extent of the nerves involved as a whole is greater than in the latter. The acute form is that in which the nerves of more vital importance, the phrenic and vagus nerves and those of the extremities, are affected early and with great intensity. In the chronic form the less vitally important nerves are affected early and intensely, but those of great vital importance escape entirely or nearly so. Honda (*Mitteil. a. d. kais. Univ.*, Tokyo, Apr., 1914).

In an experimental study of the thymus gland in pigeons and chickens with beriberi, the writers found that there was no fundamental connection between this disease and atrophy of the thymus. The latter contains but little vitamine and the benefit claimed for the administration of **thymus gland** in beriberi is probably due largely to purine and pyrimidine derivatives. Williams and Crowell (*Philippine Jour. of Sci.*, Mar., 1915).

In the majority of severe cases the quantity of urea in the blood of beriberi patients shows a marked increase. Ambard's coefficient is not infrequently high; that is, the function excreting urea is frequently disturbed. Even in cases in which the clinical symptoms are severe, if the function excreting urea is intact, the prognosis is hopeful. It is possible that cardiac failure in beriberi is due to an accumulation of some unknown toxic products in the blood, the elimination of which is coincident with

the elimination of urea. Yoshikawa, Yano, and Nemoto (Arch. of Internal Med., July, 1917).

PROGNOSIS.—The mortality from beriberi varies from 10 to 40 per cent. Death may occur from: 1, the immediate effect of the toxin upon the vital mechanism; 2, failure of the heart action, due to secondary degeneration in pneumogastric nerve and interference with action of heart from pericardial effusion; 3, suffocation from edema of lungs and pleural effusion; 4, exhaustion and occurrence of pneumonia, renal disease, and other complications arising in course of chronic cases.

In cases which do not terminate fatally, there may be partial paralysis, muscular atrophy, joint deformities, etc., for a long period, and in rare instances permanently, but the rule is complete recovery after a few weeks or months. Relapses are very common. The use of unpolished rice, however, is rapidly eradicating the disease wherever it can be enforced.

Rice bran seems to remove the cause of beriberi and prevent its development. The writers gave **bran** in the form of pills mixed with syrup and peppermint, about 40 grams (10 drams) of the bran being thus added daily to the ordinary food. As a prophylactic it was found that no case of beriberi developed among 49 native soldiers in Indo-China who took the bran, while 17.4 per cent. of 311 controls developed the disease. Breaudat and Danier (*Annales de l'Inst. Pasteur*, Feb., 1911).

Beriberi may begin slowly or suddenly. When slowly, which is usual, it is preceded by malaise, girdle pains, increasing constipation, and slowly advancing edema of the legs and face. In the rapid form the disease may become full blown over night. The progress of the disease is

equally uncertain, some becoming malignant after the disease had existed for several weeks apparently in a mild form. Again, the disease may subside in a week or continue for months. A dilated heart in 1 case cleared up completely in less than a week. All cardiac attacks come on suddenly, especially in the paraplegic stage.

Relapses, although not common, are more often found in patients used to drinking much alcohol. Cases with cardiac involvement need constant attention. In these cases the mortality may range as high as 50 per cent., while in other forms it is as low as 2 per cent. The diagnosis is not difficult when rheumatic pains, pretibial edema and analgesia are present, and the case is known to come from the tropics, where true rheumatism is rare. The knee jerks should always be tested and signs of hyperesthesia of the calf muscles sought. Doyle (*N. Y. Med. Jour.*, Apr. 8, 1916).

The disappearance of beriberi among the Philippine scouts fully supports the deficiency of vitamins theory. The disease still prevails among the civilian native population, but the military has been practically exempt since treatment has been instituted, based on this theory. The addition of a proportion of **unpolished rice, beans, etc.**, to the diet has proved a thorough success. W. P. Chamberlain (*Jour. Amer. Med. Assoc.*, Apr. 10, 1915).

TREATMENT.—Important preventive measures are the maintenance of nutrition at normal level; avoidance of exposure, dissipation or excesses; avoidance of infectious tropical disease, and, above all, the use of polished rice.

The writer reports excellent results from the use of **unpolished rice** in the Philippine Islands. Prior to February, 1910, polished rice was commonly used in the Culion leper colony. The deaths from all causes be-

tween February, 1909, and February, 1910, were 898, of which 309 were due to beriberi. From February, 1910, to February, 1911, unpolished rice was used, and there were 369, a reduction of over one-half the death rate for the previous year. It is significant that there were no deaths from beriberi during this interval following the use of unpolished rice. At the end of January, 1910, about 50 patients remained in the hospital of the colony undergoing treatment for beriberi. Each of these patients received daily, in addition to the regular food allowance, 15 grams (4 drams) of **rice polishings**, and improvement was noticed in all except 2 very advanced cases, which subsequently died. Within two weeks following this treatment, however, the cases were so far recovered as to be able to leave the hospital, and within a month all were pronounced cured. These results have been so striking that the government has drafted a bill providing for the general use of unpolished rice; that is, rice containing at least 4 per cent. of phosphorus as phosphorus pentoxide, and the levying of a tax upon polished rice which makes its sale practically prohibitive. With such an array of facts it would seem that a definite advance has been made in the study of beriberi. Heiser (Jour. Amer. Med. Assoc., Apr. 29, 1911).

Some samples of the seed of *Phaseolus lunatis*, the **golden butter bean** from the west coast of Madagascar, is one of the few beans (a cousin of the lima bean of this country) that will grow in all tropical countries, even in the dry season, and a small quantity of these beans eaten every day, with the usual rice ration of tropical peoples, will absolutely prevent beriberi. As there are at a rough calculation 100,000 deaths yearly from beriberi, the importance of a bean than can be grown in the garden of every coolie is apparent at once.

The imported beans in tropical countries are so high in price that

the average coolie is cut off from their use as a food.

Beriberi in the Japanese navy was absolutely stopped by a diet of beans. During the Russo-Japanese war the Japanese army reverted to rice only as a ration, and there were 40,000 cases of beriberi in the army. C. S. Braddock, Jr. (N. Y. Med. Jour., Apr. 1, 1916).

Large amounts of a **purée of peas** had an unmistakable curative action on beriberi. As much as 150 Gm. (5 ounces) of the purée 3 times a day was required for this, smaller amounts showing no benefit. **Oatmeal** had a similar influence, but 125 Gm. (4½ ounces) 3 times a day were necessary. Europeans did not require quite so much. Pol (Norsk Mag. f. Laeg., Jan., 1916).

Following rules recommended to prevent deficiency diseases: In any institution where bread is the staple article of diet, it should be made from **whole wheat flour**. Rice used in any quantity should be of the **brown untermilled variety**. **Beans, peas**, or other legumes known to prevent beriberi, should be served at least once a week. Canned beans or peas should not be used. Some **fresh vegetable** or **fruit** should be issued at least twice a week, and **barley**, a known preventive of beriberi, should be used in all soups. **Cornmeal** should be of the **yellow** or water-ground variety, *i.e.*, made from the whole grain. **White potatoes** and **fresh meat** should be served at least once a week, preferably once daily, as they prevent scurvy and beriberi. The too exclusive use of canned goods must be carefully avoided. E. B. Vedder (Jour. Amer. Med. Assoc., Nov. 18, 1916).

The **Norwegian gray pea** seems to be effectual in curing ship beriberi as well as Asiatic beriberi, but Pol states that the action of katjang hidjoe, better known as the *Phaseolus radiatus*, of the bean family, is more powerful. Ship beriberi never develops in the acute form sometimes observed with the Asiatic type.

With the former, edema gradually extending upward from the ankles is more common than paralysis, and proper food arrests the trouble at once. The European land type of beriberi usually runs a subacute course, and there is always paresis with or without slight edema. A healthy man with 3 healthy children developed ascending paresis which gradually became actual paralysis within 5 or 6 months. Even the organ of speech was involved. Peas were given cooked and also in the form of a decoction of 2 kg. (70 ounces) boiled down to 1 liter (quart), added to his usual food. After 17 days the paralysis began to subside, and in 2 weeks the paralysis of the legs had disappeared. Improvement was rapid for a while, then slow and gradual, corresponding to recuperation of the actually degenerative nerve cells. Traces of paresis were still evident by the eighth month. Holst (*Nederlandsch Tijdsch. v. Geneesk.*, Sept. 8, 1917).

After the disease has appeared **removal of the use of polished rice from the diet**, replacing it by unpolished rice or beans usually suffices to initiate convalescence. If the disease persists notwithstanding, the symptoms should be dealt with as they develop. The patient should be put at **rest**, a **calomel** purge given, and **liquid diet** ordered. Pain is to be combated by **hot applications**, **coal-tar derivatives**, and, if necessary, **morphine**. Should cardiac weakness persist, **strychnine**, **digitalis**, and **strophanthus** internally and **camphorated oil** or **ether** by hypodermic injection are indicated. **Acetate of potassium**, **squills**, **digitalis**, and **saline cathartics** aid in reducing edema in "wet" cases, as do also **vapor baths** and **diaphoretics**, if they do not debilitate. **Salicylate of soda**, **methylene blue**, continuous small doses of **calomel**, **intestinal anti-**

septics, and many other drugs have been recommended. **Quinine** undoubtedly benefits some cases.

The long-continued administration of **strychnine** in gradually increasing doses, until toxic phenomena appear, has been advocated.

External applications, such as the **prolonged warm bath**, **enveloping the limbs in cotton batting**, the **kaolin poultice**, **menthol**, **oil of wintergreen**, and **counterirritants**, have some use in giving comfort.

At a later period, when acute symptoms have subsided, the use of **massage** and **electric stimulation** to the paralyzed muscles is required.

Removal from damp, ill-ventilated, or otherwise unhygienic surroundings, the use of proper and sufficient food, and removal to a temperate, non-malarial climate are directly indicated, where possible.

The writers believe that in the majority of cases tropical beriberi is due to a deficiency of organic phosphates in the diet, but in occasional cases it may be due to deficient absorption of organic phosphates by the alimentary tract, or to bacterial infection possibly splitting up the phosphates before absorption, or interfering with the absorptive power of the intestine. They suggest, also, that a whole cycle of other diseases have in all probability a similar etiology, and that among these infantile scurvy, rickets, osteomalacia, etc., may be included. Lastly the writers discuss the danger of white bread to English children. White bread has given rise to polyneuritis in fowls fed upon it, and, as the phosphates are removed with the bran, it is possible that children fed largely on such bread might develop disease as the result of deficiency of organic phosphorus in the diet. It is somewhat curious that the wheat-bran rich in phosphates is given to cattle for

the purpose of fattening them. The authors advocate the substitution of whole-wheat bread for the white variety. Simpson and Edie (*Annals of Trop. Med. and Parasitol.*, Aug., 1911).

The writer treated 20 cases of human beriberi with autolyzed **brewers' yeast extract**, adults being given from 15 to 40 c.c. ($\frac{1}{2}$ ounce to 10 drams) three times a day, and children from 2 to 4 c.c. ($\frac{1}{2}$ to 1 dram) every 3 hours. Larger doses did not seem to give better results. No sign of poisoning was observed. All acute peripheral symptoms of neuritis were affected quickly. Marked results were noted in less than 3 days and a week's treatment seemed to give full relief in mild acute cases. The effect of autolyzed yeast extract was similar to that produced by the hydrolyzed extract of rice polishings, but it seemed weaker. Saleeby (*Philippine Jour. of Sci.*, Jan., 1919).

EUGENE D. BONDURANT,
Mobile.

BETANAPHTHOL is a hydrocarbon prepared from naphthalene. It occurs as a white or yellowish-white powder or in crystalline plates with a faint, phenol-like odor and a pungent taste. It is only slightly soluble in water (950 parts), freely soluble in alcohol, and readily dissolves in ether, chloroform, or solution of alkali hydroxides. It is permanent in air.

MODE OF ADMINISTRATION.—Betanaphthol is usually given in capsules, and these, if the drug is given as an intestinal antiseptic, may be coated with keratin. The dose is 2 to 5 grains (0.12 to 0.3 Gm.).

Equal parts of betanaphthol and dried sodium carbonate, thoroughly mixed, can be employed to advantage, the carbonate promoting the solution of the naphthol in water without forming with it a new compound. A 1 per cent. solution of this mixture proved able to kill, in ninety-six hours, dried anthrax spores which resisted the action of 5 per cent. lysol for ten days, and a slightly stronger solution (1.5 per cent.) destroyed

them in seventy-two hours. Against typhoid organisms and staphylococci the mixture proved to be about twice as strong as lysol. Schneider (*Zeit. f. Hyg. u. Infect.*, Bd. lii, S. 534, 1906).

PHYSIOLOGICAL ACTION.—It closely resembles naphthalene in its action. Death is caused by respiratory paralysis in animals, and toxic symptoms have been reported from its use in the human subject. Its external use has caused retinal disturbances.

In man camphorated betanaphthol may give rise to nausea, vomiting, malaise, cold sweats, purpura, and disturbance of the heat center, but the drug is quite safe if care is taken when injecting to avoid veins, and the daily dose is limited to 0.2 c.c. (4 minims) for adults, or when abscess cavities are merely swabbed out with the drug applied on lint or wool. Desesquelle (*Arch. génér. de méd.*, vol. i, p. 92, 1905).

Case of betanaphthol poisoning during treatment for ankylostomiasis was observed by the writer. In persons with diseases of the kidneys betanaphthol should be used with utmost caution, if at all. Orme (*Brit. Med. Jour.*, July 31, 1915).

THERAPEUTIC USES.—Its uses are similar to those of naphthalene. It is a good **intestinal antiseptic**, preventing fermentation and thus flatulence, and is used in **gastric or intestinal fermentation**, in **dilated stomach**, and in **diarrhea** and **dysentery**. The drug is also a **parasiticide** and valuable in **uncinariasis**. W.

BISMUTH.—Bismuth is a whitish-gray, hard, though brittle, metal, with melting point at 286.3° C., soluble in nitrohydrochloric, nitric, and hot sulphuric acids. It is very commonly contaminated with lead, iron, and copper, together with traces of arsenic, antimony, and tellurium. In the metallic form bismuth is not used in medicine, but its salts, particularly if free from impurities, are of great value.

The garlicky odor sometimes produced in the breath of patients taking the salts of bismuth is due to the presence of the metal tellurium. This fact was first noticed by Sir James Simpson, and was established further in 1875, when specimens of bismuth containing tellurium as an impurity invariably produced in the breath the peculiar odor referred to.

PREPARATIONS AND DOSES.

—The official preparations of bismuth are the following:—

Bismuth subnitrate, or *bismuthi subnitratis*, occurs as a heavy, white, microcrystalline powder, which is almost odorless and tasteless. It is nearly insoluble in water, insoluble in alcohol, but soluble in nitric or hydrochloric acid. Dose, 5 to 15 grains (0.3 to 1 Gm.).

Bismuth subcarbonate, or *bismuthi subcarbonatis*, occurs as a white or yellowish-white, tasteless and odorless powder. It is insoluble in water or alcohol, but readily soluble in nitric or hydrochloric acid with effervescence. Dose, 5 to 15 grains (0.3 to 1 Gm.).

Bismuth betanaphthol, or *bismuthi betanaphtholis*, is a compound containing about 15 per cent. of betanaphthol and yielding, on ignition, about 75 per cent. of bismuth oxide. It is a buff-colored to grayish brown, tasteless powder, nearly insoluble in water or alcohol. Dose, 5 to 15 grains (0.3 to 1 Gm.).

Bismuth and ammonium citrate, or *bismuthi et ammonii citras*, small, translucent scales having a slightly metallic and acidulous taste. It is very soluble in water, but slightly so in alcohol. It is affected by light and air, and should, therefore, be kept in

dark, well-stoppered bottles. Dose, 1 to 5 grains (0.065 to 0.3 Gm.).

Bismuth subsalicylate, or *bismuthi subsalicylas*, a white, amorphous, odorless and tasteless powder, almost insoluble in water, decomposed by alcohol, ether, and acids with liberation of the salicylic acid. Dose, 2 to 5 grains (0.13 to 0.3 Gm.).

Bismuth subgallate, or *bismuthi subgallas* (also known as *dermatol*), an amorphous, yellow, odorless and tasteless powder. It is insoluble in water and alcohol, but soluble, with decomposition, in heated hydrochloric, nitric, and sulphuric acids, and dissolved by alkalies. Dose, 2 to 5 grains (0.13 to 0.3 Gm.).

Several unofficial preparations are used:—

Bismuth citrate, or *bismuthi citras*, a white, amorphous, odorless and tasteless powder. It is insoluble in water or alcohol, but soluble in solutions of the alkaline citrates and ammonia water. Dose, 1 to 3 grains (0.065 to 0.2 Gm.).

Bismuth tribromphenolate (also known as *xeroform*) contains 50 per cent. of bismuth oxide and occurs as a yellow, nearly odorless and tasteless powder. It is insoluble in water. Dose, 10 to 15 grains (0.6 to 1 Gm.).

Bismuth nosophenate (also known as *eudoxin*), a bismuth salt of tetraiodophenolphthalein. It is a reddish-brown, odorless and tasteless powder, insoluble in water. Dose, 5 to 15 grains (0.3 to 1 Gm.).

PHYSIOLOGICAL ACTION.—

Applied to excoriated or ulcerated surfaces, the salts of bismuth exert an astringent and sedative action, but some of the salts, notably the subnitrate, salicylate, betanaphtholate, and

nosophenate, are antiseptic. They also cause drying of the secretions and form a protective covering over the wound, which thus heals under a scab that the bismuth has rendered aseptic. They have been used extensively, therefore, for the external treatment of wounds, but, as shown below, this may be followed by absorption and poisoning.

The same properties have rendered bismuth preparations, especially the subnitrate, extremely valuable in the treatment of gastric and intestinal disorders. They tend to check the gastrointestinal putrefaction of proteids, and thus prevent not only the local catarrhal disorders of the mucosa of the alimentary tract to which the products of putrefaction, including acetone and diacetic acid, give rise, but also the absorption of these acids and the resulting autointoxication. Moreover, being insoluble in the intestinal juices, they coat the mucosa and absorb what free acids are formed, thus protecting the intestinal surfaces in two ways. In addition, they neutralize the acidity of the intestinal contents and precipitate the hydrogen sulphide. Unfortunately, most bismuth salts tend to constipate by checking peristalsis, though this action becomes useful in the treatment of diarrhea and vomiting.

BISMUTH POISONING.—The prevailing view that bismuth subnitrate may be used with great freedom, both externally and internally, has been the cause of many cases of poisoning. Three classes of cases should be recognized: (1) those in which the drug is administered by the stomach or rectum as a remedy, (2) where used as a surgical therapeutic

agent, powder, paste, etc., or (3) as an aid to facilitate the X-ray examination of the gastrointestinal tract.

Poisoning in the Course of Internal Medication.—The statements of some books that pure bismuth can be taken "without injury in indefinite quantity," or that "two or three drams a day may be given to a child a year old," for example, are dangerous advice. As shown by clinical experience, even $7\frac{1}{2}$ to 15 grains (0.5 to 1 Gm.) repeated every two hours have sufficed to produce cyanosis in infants, with somnolence, and a marked garlicky odor of the breath. When the doses are larger, there appear: black- or slate-colored discoloration of the edge of the gums and of the mucosa of the mouth and gastrointestinal canal, stomatitis, gingivitis, headache, abdominal pains, vomiting and diarrhea, dysphagia, fever, delirium, deepening of the cyanosis with dyspnea and hypothermia, diminution in the amount of urine, methemoglobinuria, albuminuria, nephritis, hiccough, collapse, and even death. Where an idiosyncrasy exists in the adult 15 to 20 grains (1 to 1.3 Gm.) sufficed to produce toxic phenomena, including an eruption resembling that of scarlatina (Dubreuilh). Mathieu has observed under very large doses in adults a pigmentation resembling the chloasma of pregnant women.

Acute poisoning by subnitrate of bismuth in a woman aged 22 years suffering from tuberculous stenosis of the small intestine. She had been in the habit of taking subnitrate of bismuth in doses of from 15 to 30 grams. She developed symptoms much like those of methemoglobinemia, such as difficulty of the respiration, convulsions, a subnormal

temperature, and intense cyanosis. The patient was in a very grave condition for two days, but, nevertheless, recovered. Bensaude and Rivet (*Lancet*, Feb. 20, 1909).

Subcutaneous injections have been found to produce stomatitis with erosions and sloughing, albuminuria, enteritis with bloody stools, and slight hepatic congestion.

Rectal injections of bismuth subnitrate in emulsion are even more dangerous than when the salt is administered orally.

All these toxic phenomena having been obtained with the subnitrate, Böhme (1905) ascribed them to the nitrites produced and absorbed from this salt. The feces were found capable of reducing nitrates to nitrites, a process facilitated by pronounced bacterial activity. Poisoning is of course liable to occur, therefore, in subjects of all ages, but especially in children suffering from intestinal putrefaction. This form of intoxication is admittedly not due to the metal bismuth, but to the special salt bismuth subnitrate. In the light of this view it is preferable to employ a different salt, such as the carbonate, when large doses are required. Lewin (1909), on the other hand, ascribes the toxic effects to the absorption of bismuth as a sulphide, but Böhme's view has been sustained by other investigators.

Sudden death of an infant who had been given bismuth emulsion by the mouth, and, after an interval of two days, several grams by the rectum. Three hours after the rectal dose she was seized with abdominal pains and diarrhea, accompanied by steadily increasing cyanosis and marked dyspnea. The heart was markedly overacting and the pulse small and feeble. Death occurred in half an hour. At

the autopsy traces of nitrous acid were found in the blood and pericardial fluid, though no metallic bismuth was found in the blood or liver. The writer, by chemical means and by experiments on animals, established that nitrites can be formed from bismuth subnitrate in sufficient quantities to cause death. He found that human feces, and especially those of infants, were capable of reducing nitrates to nitrites. Böhme (*Arch. f. exp. Path. und Pharm.*, Bd. lvii, S. 441, 1907).

Poisoning when Used Locally.—

The local application of bismuth subnitrate in the form of powder to burns, excoriated surfaces, etc., or in that of emulsion or paste into cold abscesses, fissures, fistulas, etc., has also given rise to untoward effects followed in some instances by death. Sprinkled over burns of the second or third degrees, for example, the subnitrate forms a scab-like layer which protects the lesion well enough, but which, however, does not prevent the gradual absorption of the drug or its components into the blood. Gingivitis with the slate-colored line and stomatitis characterized by more or less pain and swelling may then appear, followed by the above-described toxic phenomena and even death if the quantity absorbed be sufficiently large.

Case of a delicate woman who was treated with a 10 per cent. bismuth salve for a burn. After a few weeks she began to show signs of bismuth poisoning and a nephritis. The case ended fatally. At the autopsy, the mucous membrane of the entire colon was found to be stained black. The cause of the poisoning in this case is ascribed by the author to the extensive areas on the body deprived of cuticle to which the salve was applied. Mahne (*Berl. klin. Woch.*, Feb. 27, 1905).

The introduction of bismuth paste by Beck for the treatment mainly of tuberculous sinuses, infected abscesses in Pott's disease, etc., while rendering signal service therapeutically, has, nevertheless, been followed by quite an array of toxic cases. The earliest symptom of the chronic form of poisoning, due to the slow and prolonged absorption of bismuth by a suppurating surface, is a pale, livid tint of the skin. This is followed by an eruption of small, bluish ulcers on the gums. The further progress of the poisoning is marked by nausea, headache, vomiting, and albuminuria. In advanced cases the ulceration of the gums increases, and the patient becomes emaciated, and gradually succumbs.

Beck, who in his own practice observed cases of the kind, states that the bad results may be prevented by constantly **looking out for** the appearance of the **early signs** of the poisoning, and if any of these be manifested by injecting into the cavity still occupied by the bismuth paste some warm and **sterilized olive oil**, which is allowed to remain from twelve to twenty-four hours, *i.e.*, until it has formed an emulsion which can be removed by aspiration.

Preliminary report of 2 cases in adults showing that toxic effects may result from the use of moderate amounts of bismuth-vaselin paste. Conservatism should govern its use until further study establishes more clearly the limit of non-toxic dosage, the manner of its absorption, and the possibility of bismuth idiosyncrasy. V. C. David and J. R. Kauffman (Jour. Amer. Med. Assoc., March 27, 1909).

In the course of the last year many instances have been recorded of serious and, occasionally, of fatal results

from the use of bismuth paste in the local treatment of suppurating cavities and fistulæ. Reich, of Tübingen, has collected 16 cases, with 7 deaths, and of 3 cases recently put on record by Matsuoka 2 were fatal. Beck (Centralbl. f. Chir., Nu. 17, 1910).

It should be recognized that bismuth paste has its dangers, and if we can find an entirely innocuous substance to replace it we shall do well to make the change.

Personal case: G., 3 years old. Diagnosis: Caries spinalis thoracis, of about one year's duration, with well-marked kyphosis and freely discharging sinus in the right lumbar region. The abscess was opened April 12, 1911. July 7, 1911, an injection was made into the sinus, consisting of the regular bismuth paste mixture, 1 part bismuth subnitrate to 2 parts vaselin. July 9th. A sharp rise in temperature, to 103° F., followed the injection. August 24th. The temperature soon subsided, and the child did well thereafter. An injection of about 2 ounces of the paste was then made. August 26th. A sharp febrile reaction again followed the injection, reaching 103° F. September 15th. The temperature soon subsided, and has since run between 97.5° and 99.6°. About 2 ounces of the paste were injected. September 19th. The injection was followed by the usual rise in temperature, which slowly subsided. September 30th. The abscess almost healed. The patient has a blackish discoloration on one side of her tongue, but seems in fairly good condition. October 5th. The child has been vomiting constantly, has lost weight steadily, can keep nothing on her stomach, and is very restless. October 8th. Eight c.c. of olive oil were injected into the sinuses. October 9th. Rectal feeding begun and continued to the end. The temperature does not run above 100° F. October 14th. The patient is growing steadily worse, and refuses all food. Ulcers on both sides of the mouth, between the cheek and alveo-

lar process, are spreading rapidly. Some little discharge of bismuth followed the injection of 8 c.c. of olive oil. The temperature is practically normal, and pulse runs about 120 to 130. The mouth is dry and brown. The child is emaciated, sleepless, and tosses her head about. The blackness of the tongue has persisted and increased. October 17th. Two bloody stools. Death. L. W. Ely (Med. Rec., Jan. 20, 1912).

After an analysis of the literature of poisoning from the injection of *bismuth paste* into the thoracic cavity, the writer states that the indiscriminate use of bismuth, even as a dressing for an external wound, is not devoid of danger, as illustrated by a personal case. A review of the literature showed that up to 1916 there have been 43 reported cases of intoxication, 13 of them fatal, following the local application of bismuth to granulating surfaces. W. H. Higgins (Jour. Amer. Med. Assoc., Feb. 26, 1916).

Case of rather severe bismuth poisoning occurring from the injection of about 45 c.c. of Beck's paste into a discharging sinus. Irrigation of the sinus with warm olive oil removed the bismuth and patient soon made a good recovery, except that some pigmentation of the gums and tongue persisted. Freilich (Jour. Amer. Med. Assoc., Jan. 13, 1917).

Five men had shown symptoms suggesting plumbism, and all had had septic wounds. Four developed a blue line on the gums, and complained of sore mouths. Bluish pigmentation was found in some cases on the inside of the cheeks. Anemia was present in all cases, and disappeared as soon as the wounds healed. Constipation was also present. There was no wrist-drop, colic, headache, or neuritis. Blood cells showed no granules. The urine was examined for lead but no trace was found. The evidence pointed to poisoning from bismuth or iodoform. The presence of the blue line pointed strongly to

bismuth reaction. F. A. Hepworth (Lancet, Apr. 14, 1917).

Beck states that the use of bismuth paste is contraindicated in cases of acute suppuration, particularly empyema, as absorption so readily occurs on the fresh inner surface of the suppurating pleura. On the other hand, in old abscess cavities with thick and fibrous walls with much diminished capacity for absorption, the paste may be applied with but slight risk. The maximum strength of the paste used by Beck is 33 per cent. When the secretion becomes sterile, the paste is withdrawn, and replaced either by a 10 per cent. paste or by sterilized vaselin.

Poisoning from Use in X-ray Examination.—Since arsenic-free bismuth has been available, the subnitrate has been extensively used to facilitate X-ray examinations of the gastrointestinal tract, owing to the fact that, being impermeable to the rays, it causes the organ containing it to stand out prominently in the shadow test. Unfortunately, large quantities are necessary to obtain satisfactory results, and it is because of this that many cases of poisoning have occurred, absorption taking place from the intestine after decomposition of the salt. The symptoms are those already described; they appear from one to four hours after the use of the salt. Nausea, vomiting, marked cyanosis, prostration, and rapid respiration may all occur, last several hours, and the case proceed to recovery, especially if the poison is removed. In unfavorable cases methemoglobinemia and the other symptoms described appear in rapid succession until death occurs.

In 1906 Benneke and Hoffmann reported the death of an infant who had been given 3 to 4 grams of bismuth in 100 c.c. of buttermilk; it was supposed that the poisoning was due to some chemical change caused by the lactic acid, though this did not explain the methemoglobinemia found at autopsy.

The writer's own case was a man aged 20 years. Three hours after a dose of 50 grams of bismuth subnitrate, given for radioscopic examination, he suddenly became markedly pale and cyanosed, with all the symptoms of collapse. He was freely stimulated, but died in a few hours. There is also an account of 3 other cases that recovered after alarming symptoms of similar nature. To prevent this the writer advises that bismuth carbonate be used. Meyer (*Therap. Monatsh.*, Bd. viii, S. 388, 1908).

Case of a man who had jabbed a pitchfork into his left knee. The knee became so swollen and red that it was necessary to open the joint and drain. Because of a persistent sinus following incision, a month later this was injected with bismuth paste. The sinus closed over, but 5 weeks before death the patient began to complain of sore mouth, which continued to get worse until he died. The blood examination on admission showed 3,900,000 red cells, 30,000 white cells, and 70 per cent. hemoglobin. At first the case was thought to be one of *cancrum oris*. After about 10 days the slough in the mouth separated, leaving a bleeding surface. There could then be made out a definite pigmentation of the mucous membrane and a line about the teeth.

A röntgenogram of the knee revealed a large quantity of bismuth imbedded in the knee joint and crural bursa. Two other cases illustrate nitrite poisoning from bismuth subnitrate. A 4-year-old child was given a dram (4 Gm.) of bismuth subnitrate in a starch enema because of colitis. Twelve hours later she became nau-

seated, very cyanosed, with pulse small and weak, and partial coma supervened. The blood was very dark. The colon was irrigated repeatedly and injections of camphor given hypodermically, and within 24 hours she was much better. A man, aged 50, had been given an ounce (30 Gm.) of bismuth subnitrate in milk for X-ray gastric examination. During the night symptoms of poisoning appeared, and persisted for 3 days. J. Phillips (*Cleveland Med. Jour.*, June, 1917).

TREATMENT OF BISMUTH POISONING.—Prophylaxis imposes the use of smaller doses than have been the rule. The doses mentioned under "Preparations and Doses" at the beginning of this article should be approximated and adjustment made to the age of the patient. The surgical use of bismuth, whether in powder or paste, is subject to the same rules, unless care be taken not to leave it on or in the tissues sufficiently long to permit the absorption of enough bismuth to bring on toxic symptoms. If any appear, the drug should at once be removed by prolonged warm bathing of the encrusted surface or injection of **warm vaselin and aspiration** when dealing with cavities.

For X-ray examination, the stomach or rectum should be carefully washed out and all bismuth removed as soon as the skiagraphic exposure is terminated, following up the colonic irrigation by a saline purgative.

Poisoning caused by the use of large doses of bismuth in the shadow test with the X-rays observed by the writers.

Whatever be the cause of these accidents, it behooves the physician in the future to use every precaution to prevent dangerous results arising from the administration of large doses of bismuth. Worden, Sailer, Pan-

coast, and Davis (Univ. of Penna. Med. Bull., Aug., 1906).

The writer employed bismuth carbonate instead of subnitrate in Roentgen examination of a woman suspected of cancer. Thirty hours after taking the injection the greater part could be seen in the rectum and the patient complained of pains and tenesmus and the left hypochondrium was tender. After the rectum had been evacuated by an enema, the stool showing considerable blood, the symptoms subsided. The bismuth carbonate had evidently accumulated as an irritating foreign body in the rectum. The case illustrates the importance of clearing out the intestine and not allowing the bismuth to accumulate therein. Metzger (Med. Klinik, June 4, 1911).

THERAPEUTICS.—The most important therapeutic application of bismuth has been in **gastrointestinal disorders**, ever since Trousseau demonstrated its great value in these affections. While the use of the massive doses recommended by various authors has clearly shown that bismuth is not free of toxic effects, thus somewhat lessening its use, the fact remains that in judicious doses it is worthy of the greatest confidence, particularly in the various forms of dyspepsia. As recently emphasized by Hayem, bismuth is especially valuable in all cases of painful **gastritis**. It acts favorably on **gastrorrhagia** and it also reduces **abnormal fermentations**. Owing to its chemical effect upon hydrochloric acid, it has been especially employed in the condition of **hyperchlorhydria**; but as shown by Hayem, it can be used with equal success in **hypopeptics** and even among **apeptics**. The improvement is prompt and the relief very marked in all cases of **painful gastric crises** (early or late pains, cramps, burnings, in-

tolerable pains, sensations of weight, uneasy feelings, unseasonable pangs of hunger, etc.). In severe cases it may be impossible to give the bismuth at the beginning; but as soon as the acute period has passed, it can be exhibited with the most favorable results. Its calming effects are obtained generally during the second or third day of treatment, but more frequently not until the sixth day. In **nervous dyspepsias**, and in gastric crises of central origin, only temporary relief can be looked for. In **gastric ulcer**, its use has become classic; it relieves pain, stops reflex irritation, and its protective properties favor rapid healing of the lesion. Even in **cancer of the stomach**, its beneficial effects are sometimes remarkable in relieving pain, but they are only temporary, and the patients are obliged to take it constantly. This very fact of its long-continued use is an indication of cancer of the stomach, which of itself may have some value in a case of difficult diagnosis.

[It is a question whether the analgesic property of bismuth subnitrate is not due to the poisonous effects of liberated nitrites, *i.e.*, to a poisonous action. This is suggested by the facts that large doses are alone effective, and that the subnitrate of all the bismuth salts alone relieves pain to any material degree. The physiological action of the nitrites being to dilate the arterioles throughout the entire body, the general blood-pressure is relieved and the congestion of the painful area likewise, thus diminishing temporarily its sensitiveness. C. E. DE M. S.]

If it becomes necessary to administer more than 40 grains (2.6 Gm.) three times a day—suspended in water—to relieve the pain of gastric cancer it is preferable not to increase

the dose, but add thereto either codeine, morphine, or cocaine.

Dyspepsia attended with hyperacidity, irritable stomach, and **gastric cancer** is often happily influenced by the following powder:—

R *Subnitrate of bismuth*,
Carbonate of magnesium of each 5 grs. (0.33 Gm.).
Morphine sulphate .. ½ gr. (0.005 Gm.).

M. For 1 powder.

Acute or chronic diarrheas are often relieved by bismuth. A dose of castor-oil in advance of bismuth subnitrate is of value in removing any possible cause of irritation.

In severe **infantile diarrhea** it is best to commence with a dose of 3 to 5 grains (0.2 to 0.33 Gm.); it is then possible to dispense entirely with opium in many instances. The drug can be administered to children in a mixture with glycerin and water, to be shaken before ingestion. The powder form should be avoided, as it is liable to produce irritation of the gastrointestinal mucous membrane.

Many cases of **vomiting**, even the **vomiting of pregnancy**, will usually yield to the administration of 10-grain doses of one or other of the bismuth salts. It is not always tolerated by the stomach when given in larger doses. This drawback may be in a measure obviated when necessary by combining it with an aromatic powder or magnesia. The formula given above under "dyspepsia" is of great value in such cases.

Lion recommends that, in cases of **pulmonary tuberculosis** with coughing and vomiting after meals, 20 grams (300 grains) of bismuth subnitrate be given in two-thirds of a glassful of water one hour before a meal. Usually after the very first dose the vomiting is entirely pre-

vented, and if the treatment be kept up ten or twelve days it will cease permanently. Occasionally the cough provoked by taking food persists, but it is no longer followed by vomiting. H. Paillard (*Progrès méd.*, Jan. 27, 1912).

[The above abstract illustrates the dangerous recklessness with which bismuth is used owing to the prevailing belief that it is a harmless agent. Such enormous doses are not necessary to prevent the above form of emesis. C. E. DE M. S.]

The color of the stools is changed to a blackish or slate-like hue when bismuth is administered, but this need give rise to no anxiety.

The salicylate of bismuth, the dose of which is smaller, is very efficient in **infantile diarrhea** in doses of 1 to 2 grains (0.065 to 0.13 Gm.). It has also been used in the diarrhea of **typhoid fever**, but the betanaphtholate is generally preferred, owing to its greater antiseptic activity. Both salts may be administered together, however, with advantage, according to some authors. The double salt of bismuth and ammonium citrate is also valuable in **acute and chronic diarrhea**. This applies also to a marked degree to bismuth subgallate, but in 5- to 10-grain (0.33 to 0.66 Gm.) doses three times daily.

Local Use of Bismuth Preparations.—The toxic effects of bismuth subnitrate when applied as a dusting powder to exposed surfaces have somewhat reduced the use of bismuth salts in surgical disorders, but if it is remembered that it is the subnitrate that has given rise to the untoward effects reported it is only necessary to limit its use to small **excoriations, ulcers, burns**, etc., to avoid such effects. Or, the subcarbonate may be

used instead. The tribromphenolbismuth (xeroform) has been found to replace iodoform advantageously in the above and other surgical disorders, especially in **infected wounds, ulcers, and in uterine erosions.** The subnitrate or subcarbonate of bismuth is extensively used also as dusting powder in the treatment of various skin disorders, especially **erythema, vesicular eczema, acne, and intertrigo.**

For the treatment of **fistula** of various kinds, those, for instance, following **empyema, mastoid disease, tuberculous abscesses, tuberculosis of the spine and joints, resection, etc.,** Emil G. Beck's bismuth paste has been extensively used with excellent results when the lesions were not too extensive or too far advanced. The subnitrate having caused poisoning in many cases, as we have seen, the subcarbonate may be used instead, though it does not entirely avert the untoward effects, unless the quantity recommended is somewhat reduced. J. C. Beck's main mixtures, used in 319 cases, are as follows: (1) A paste containing 33 parts of bismuth subnitrate and 67 parts vaselin, which is used principally in the localities where the idea is to cover rather than distend and as a local treatment of the nasal mucosa in **hypertrophic rhinitis.** (2) A paste containing 30 parts bismuth to 60 of vaselin and 5 parts each of white wax and paraffin, which is of almost universal application, except for filling the defect of simple **mastoid operation,** where a paste containing less vaselin and double the above amount of white wax and paraffin is used. (3) A still stiffer paste of 30 parts bismuth, 35 parts vaselin, 25 parts paraffin, and 10

parts white wax, used only in the radical **frontal sinus operation** to act as a plug. The syringe used is a powerful instrument working on the thread principle. The flexible tube is essential and must be of metal, as rubber distends and soon breaks. Beck believes that in the first place either the bismuth or the nitrate, coming in contact with the tissues, produces such a change in the inflammatory cells and leucocytes of the infected area that they are enabled slowly to destroy the vegetable organisms. Another factor to be considered is the coating effect of the bismuth to the mucous membrane, and his experience has convinced him as to its advantages as a dressing. The cases should be closely watched, and if any indication of poisoning appears the paste should be softened with warm vaselin and aspirated, and the cavity washed out.

Report of two very satisfactory cures of **hydatid sinuses** of some duration by Beck's method. So far as the author is aware, it had not previously been tried in hydatid sinuses in Adelaide. Bollen (*Austral. Med. Gaz.*, May 20, 1910).

Use of Beck's bismuth paste in 10 cases of **fistula** resulting from removal of a tuberculous kidney and another of a fistula with a simple pyonephrosis with concretions. The paste used was a mixture of 10 parts of bismuth with 10 parts each of paraffin and lanolin and 20 parts of vaselin. The amount injected was only from 5 to 10 or 12 c.c. except in a single case. In other points Beck's technique was followed. Although such striking results as Beck has reported were not observed, yet the treatment is deemed valuable. A cure was attained in some cases in which the process had proved rebellious to other measures. Heitz-Berger and Moreno (*Annales des*

mal. des org. genito-urin., June 1, 1910).

Failures of bismuth paste to cure are due to the following causes: 1. The bismuth is not sufficiently incorporated into the petrolatum, leaving large masses of pure bismuth. 2. Water accidentally gets in and makes a mass like curdled milk. 3. The mixture is not heated sufficiently before injection. 4. Improper instruments are used. 5. Undue force is used; the paste must be forced in very slowly. 6. The sinus is incompletely filled. 7. The sinus is injected too frequently. 8. The patient is allowed to dress his own wounds. Two bacterial examinations should be made, one before and one after injection; if the second is negative, they must not repeat the injection. Finally, the wound should be dressed daily. E. G. Beck (N. Y. Med. Jour., June 17, 1916).

For dispensary patients the writers use a paste prepared according to the formula of Morison and an emulsion containing bismuth subcarbonate, 1 part; iodoform, 2, and liquid petrolatum, 4. In highly infected wounds they irrigate with sterile saline or 4 per cent. boric acid, swab thoroughly with 75 per cent. alcohol, shave and cleanse the skin with the alcohol, pack the wound and all sinuses and pockets tightly with the paste, and close it with silk or silk-worm gut sutures. Most of such wounds heal by first intention and leave insignificant scars. Tuberculous cervical adenitis with suppuration responds promptly to curettage followed by alcohol and the bismuth paste. Empyema cavities and lung abscesses also close promptly when filled with the emulsion and with the drainage tube in place. No cases of poisoning have so far resulted. O'Connor and Kreutzmann (Jour. Amer. Med. Assoc., Dec. 15, 1917).

The technique is being somewhat modified by other observers. While Beck fills the fistula by injecting the paste forcibly into the mouth of the

cavity, Brandes passes a rubber tube or catheter into the fistula to its bottom and injects the paste through it. In this way driving of the exudate into the surrounding tissues is avoided. He frequently fills only the bottom of the fistula to avoid intoxication. The addition of iodine has been found to enhance the efficiency of the paste in the treatment of **cancerous fistula**.

In a case of **discharging sinus** associated with breast cancer the author, after using Beck's bismuth paste and other classic preparations without success, made the experiment of adding to Beck's paste some iodine tincture. After 3 injections, made within ten days, the sinus closed. The preparation was later used in other cases with very satisfactory results. It was made up of: bismuth subnitrate, 30 Gm. (1 ounce); petrolatum, 60 Gm. (2 ounces); white wax and paraffin, of each, 5 Gm. (80 grains), and iodine tincture, 2 Gm. (30 minims). The iodine tincture is added after the other ingredients are thoroughly mixed, and the paste is to be well stirred whenever used. Where the amount to be used is large the proportion of iodine may be reduced in order to avoid excessive absorption and phenomena of intoxication. L. D. Green (Cal. State Jour. of Med., Dec., 1911).

L. T. DE M. SAJOUS,
Philadelphia.

BLASTOMYCOSIS.—DEFINITION.—Blastomycosis is a chronic disease involving usually the skin, occasionally the lungs or other internal organs, caused by some form of blastomycetes, a parasitic fungus.

Our knowledge of this disease began in 1894, when Gilchrist found that a supposed case of verrucose skin tuberculosis was in reality due to a yeast or mold fungus developing in the skin. Busse in the same year reported a case in which the lungs, lymphnodes, spleen, kidney, and bones were similarly involved, with a fatal

termination. Since that time increasingly numerous cases have been reported from Europe and in the United States, and according to Castellani and Chalmers, the disease is common in Southern India and Ceylon, the Philippine Islands, Indo-China, as well as, probably, in many other tropical regions. Within the United States, more cases have so far been reported from Chicago and its vicinity than from any other district.

SYMPTOMS.—The history and appearance of blastomycotic skin lesions suffice, in most instances, for a diagnosis. The lesion begins as a papule, which soon becomes a pustule. The surrounding skin then becomes inflamed and numerous abscesses of pin-head size are formed at its surface. The diseased patch becomes raised $\frac{1}{4}$ to $\frac{1}{2}$ inch above the surrounding skin and acquires steeply inclined margins. The contents of the small abscesses, which is glutinous and opaque, includes an abundance of the blastomycetes, which are seen also in sections of the involved skin. When the abscesses have emptied the skin exhibits a rough, uneven, "papillomatous" appearance, due to prolonged persistence of the solid partitions between the abscesses. When these break down, the appearance of the ulcer is less characteristic. Or, the abscesses may originally have been located at a greater depth in the skin, or subcutaneously, and the skin surface have become involved secondarily.

The history in cutaneous blastomycosis is typically initiated by an abrasion, cut, or other injury of the skin. After the latter has been involved exclusively for some time, perhaps for several years, the blastomycetes may enter the lymphatics or blood-stream and become disseminated in the general system. The lymphnodes become inflamed and form abscesses. Soon the lungs become involved—or, as is known to occur in a considerable percentage of cases, the lungs have been primarily affected, the original portal of entry having been the respiratory tract. The symptoms of lung involvement are cough, mucopurulent expectoration—sometimes blood-streaked—mucus, fever, night sweats, and marked prostration. The bones and joints may become affected. Usually the skin lesions run a

somewhat more rapid course after the lungs have become involved. The lung involvement generally presages a fatal ending. On the other hand, while the lesions are confined to the skin they are usually curable.

Case of blastomycosis of the skin in a patient aged 46 years. It had appeared 8 years before with lesions suggesting pustules, or boils, in the left axilla. After six months of futile therapy the entire lesion-bearing area was excised. After three years' respite the lesions appeared in the opposite armpit, and some months later in the groins, extending directly to the scrotum and anal furrow. There was at no time any ulceration, although the continuous secretion through minute sinuses was offensive. Gradually the general health became impaired. Persistent study of the secretion eventually led to obtaining a pure culture of yeast cells. Dörscher (Corresp. blatt f. schweizer Aerzte, Sept. 29, 1917).

The writer classifies the cases of blastomycosis he has seen into: (1) cutaneous type, (2) muco-cutaneous type, and (3) gluteal blastomycosis. The cutaneous type is characterized by verrucose patches with minute abscesses, and is quite common in Ceylon and other tropical countries. The muco-cutaneous type attacks not only the skin but also the oral mucosa and the pharynx, giving rise to numerous small papillomatous or frambesiform patches, which later may ulcerate. Gluteal blastomycosis presents a diffuse induration with numerous openings from which a thin purulent liquid exudes. Fungi of the genus *Saccharomyces* or *Monilia* are generally isolated from the pus. Castellani (Lancet, i, 847, 895, 1920).

ETIOLOGY AND PATHOLOGY.—

The vegetable organism causing the disease is a mold fungus which propagates by budding and is thus distinguished from the organism of "coccidial granuloma," which multiplies by endosporulation. The blastomycetes is a spherical body, unless observed during the process

of budding, when there may be seen a secondary node varying from a slight protrusion from the mother cell to a completely formed new cell ready to be cast off. No mycelium is seen in the tissues, but an abundant growth of it develops on culture media.

Among 47 American cases collected by Wade and Bell, the parts diseased, other than the skin, included the lungs, bones, spleen, kidneys, liver, lymph nodes, meninges, pleuræ, prostate, retropharynx, larynx, heart, peritoneum, pericardium, pancreas, adrenals, muscles, intestinal tract, epididymis and testicle, eye, tongue, tonsils, trachea, esophagus, and diaphragm. In lung involvement, there is little or no tendency toward cavity formation.

Report of cases unusual from the pathologic point of view. In 1 case there were extensive lesions of the spleen and liver, apparently due to the blastomyces, in which very few yeast cells could be found. In a second case there was an apparent secondary invasion by the blastomyces of a pellagrin suffering from pulmonary tuberculosis. In the skin lesion very interesting minute forms were found and specially studied. In a third case the heart was extensively involved, the condition being apparently unique. Widespread secondary bacterial invasion was noted in the liver, brain and bones. In a fourth case there was involvement of the lungs, liver, kidneys and lymph-nodes, cutaneous and subcutaneous. In the fifth case the lungs, ribs, vertebrae and spinal cord were involved with the cutaneous and subcutaneous nodules present. Wade and Bell (*Arch. of Internal Med.*, July, 1916).

Report of a case of blastomycosis observed in Italy. The lesions, located in the mucosa of the mouth, pharynx, and larynx, were similar to those of the special Brazilian form of blastomycosis of the oral mucosa described by Lutz under the name of Brazilian zymonematosi. Treatment with iodine resulted in complete recovery. Brazilian cases usu-

ally end fatally. G. Basile (*Policlinico*, xxiv, sez. chir., 88, 1917).

DIAGNOSIS.—A positive diagnosis is based on demonstration of the blastomycetes in the pus from the skin or other lesions or in the sputum. The organisms are easily overlooked in stained preparations.

Coccidial granuloma, reported chiefly from California, is distinguished clinically from blastomycosis in being always systemic and nearly always fatal. It runs a more rapid course. The skin lesions fail to show the miliary abscesses of blastomycosis and in many instances appear to be secondary to the internal disease. Culturally, coccidial granuloma exhibits a circular, compact growth with sharp edges, while blastomycotic culture fades gradually into the surrounding medium.

Sporotrichosis, caused by a somewhat similar fungus, is distinguished clinically by primary involvement of the lymphatics, with secondary involvement of the skin and development of superficial abscesses along the course of the lymphatic vessels. The abscesses may be several inches apart and form a chain extending the entire length of an arm or leg.

Tuberculosis is clinically distinguished in that it most commonly affects the lungs, while blastomycosis most commonly affects the skin. Pulmonary blastomycosis runs a more acute course than lung tuberculosis, and sputum examination is diagnostic.

Of 29 collected cases, two-thirds occurred under the age of 34 years and all but 2 were in men. In at least 14 cases, the first symptoms were referable to the lungs, suggesting the respiratory tract as the usual route of infection. Pulmonary symptoms occurred sooner or later in all cases. **Vaccination** with a filtrate or suspension of triturated membranes of the organism, grown at room temperature in bouillon for 2 to 6 months, was practised in 2 systemic cases.

A von Pirquet test performed with the suspension was found of diagnostic value, a distinct papule, persisting 4 days, being produced. A.

M. Stober (Arch. of Internal Med., Apr., 1914).

TREATMENT.—According to Stober, the influence of food, climate, and hygiene is important in the treatment. **Potassium iodide** in large doses seemed to cure one of Stober's 3 patients who recovered. For the *cough, pain, and insomnia*, **codeine** is especially valuable. **Excision of skin lesions and aspiration and drainage of abscesses** give good results. Solutions of **copper sulphate** and **iodine** have proven useful for irrigation of abscesses. Treatment consisting of **potassium iodide** internally, and a **local antiseptic** and the **X-rays** externally, was found promptly curative by W. Frick in a case involving the nose and upper lip.

In a case of blastomycosis of 3 months' duration and involving both lids of the left eye, a **radium** varnish applicator, one-quarter strength, containing, 0.04 Gm. ($\frac{3}{8}$ grain) of radium barium salt, was applied for a total of 3 hours in fractional doses during the course of 3 weeks and caused the painless disappearance of the lesion. Two minute points appeared after a few weeks, but disappeared after 15 minutes' exposure to the radium. F. E. Simpson (Jour. Amer. Med. Assoc., Mar. 14, 1914). S.

BLAUD'S PILL. See IRON.

BLEEDERS' DISEASE. See HEMOPHILIA.

BLEEDING. See VENESECTION.

BLEPHARITIS AND BLEPHARADENITIS.—DEFINITION.

Blepharitis is a symptom which can best be defined as an inflammation of the Meibomian, or sebaceous, glands of the hair-follicles of the eyelids, and, secondarily, of the follicles themselves. It may occur as the expression of local external irritation or reflex irritation from refraction errors, or may accompany conjunctival irritations, stricture of the tear-ducts, and inflammations of all sorts.

SYMPTOMS.—More or less redness with slight localized swelling at the edges of the lids is the first manifestation of the disease. This gradually spreads until the entire edge of the upper lid is involved. Crusts appear later around the bases of the cilia of the swollen part, and, the secretions being more or less infectious, gradual extension to the lower lid follows. Some of the cilia in the inflamed follicles become loosened, and may easily be withdrawn without causing pain, or they fall or are forced out imbedded in the crusts, which cause itching and so often are picked out.

Chronic conjunctivitis, phlyctenular conjunctivitis, and trachoma frequently occur as concomitants or complications.

ETIOLOGY.—Blepharitis is more common in strumous individuals. It frequently presents itself as a reflex symptom, the result of excessive use of the eyes for close work, etc. Apart from the parasitic and traumatic varieties of blepharitis, it is usually of reflex origin, due to uncorrected refraction errors. As a rule, blepharitis ciliaris may be regarded as a sort of optical barometer or as an expression of the amount of functional strain; this is made manifest by a more or less intense variety of blepharitis or blepharadenitis (chronic blepharitis), and in my experience usually accompanies errors of refraction *other than myopia*.

So-called "styes"—hordeola—accompany blepharitis, and, with retention cysts and tarsal tumors, are the result of blepharadenitis or chronic blepharitis, with stenosis or stricture of the excretory ducts and

acute and chronic abscesses of the Meibomian glands as a sequence. The varieties are:—

1. Blepharitis ciliaris: simple; caused by reflex refraction errors.

2. Blepharitis ciliaris: marginal and ulcerative, chronic, conjunctival, trachomatous, diphtheritic, stricture of lachrymal duct, etc.

3. Blepharitis ciliaris: eczematous, squamous, exudative, pedicular.

4. Blepharitis ciliaris: furunculous, infectious, autoinfectious.

5. Blepharitis ciliaris: exanthematous, erysipelalous, phlegmonous, traumatic.

6. Blepharitis ciliaris: blepharadenitis, chronic Meibomian and follicular inflammation and obstruction.

PATHOLOGY.—If the crusts are soaked and carefully washed off and the bases of the lashes are magnified and carefully examined, it will be seen that the mouths of the follicles no longer closely surround the cilia. The latter are thus loosened. In more advanced cases the hair-follicles are destroyed by the inflammatory process and the lashes are lost and are no longer reproduced, the seat of their former implantation becoming exuding sacs or bare cicatricial tissue. The loss of the protection afforded the eye from light and the mucous surfaces of the lid, by the cilia, increases the sources of irritation and inflammation; involvement of the lachrymal puncta may then give rise to lachrymations, epiphora, eversion of the lid, closure of the duct, and conjunctival and corneal inflammations follow as formidable complications.

PROGNOSIS is good in the majority of cases where true prophylaxis is employed. Congestion of the edge of

the lids, with slight swelling, if reflex, is a condition which is promptly cured if judiciously treated (*i.e.*, if the eyes be properly refracted by atropine, the only mydriatic). If this refracting has not been done properly the conditions often intensified, instead of being relieved, are a proof of correctness. The chronic or ulcerative form is less easily mastered, and the complications that are likely to follow make it important that blepharitis receive attention in its early stages.

TREATMENT in all forms of *blepharitis marginalis* depends for its success upon prophylaxis, and this is not possible without thorough drainage of the eye. In the first and second varieties the crusts must be carefully soaked and mopped with a warm, **alkaline solution** in the hands of the patient until softened. They should not be forcibly removed. Pledgets of absorbent cotton should be used to sop or mop the crusts and not disturb the cilia, which are ever ready to drop out. This tedious soaking process seldom occupies less than half an hour. In **softening the crusts** the head should be held erect and the basin containing the solution held under the chin; otherwise, the blood by gravity congests the tutamina and partially defeats our purpose. The pledget of wet cotton should be held between the thumb and forefinger only, of the hand on the side to be soaked. If the back of the hand be kept uppermost and the other three fingers extended, the solution will **not** run down the arm nor wet nor soil the patient.

Having thoroughly removed the crusts, carefully dry the margins of

the lids. In ten minutes' time **wipe dry** the edges of the lids, repeat this procedure several times, and remove the fresh fluid exudate, which, if allowed to remain, dries and forms new crusts, and under these conditions all local remedial applications are of little use. They simply do not reach the infected, exuding area. This treatment must be persisted in, and requires the utmost patience. The **yellow ointment** of Pagenstecher has stood the test of years, and when this ointment will not effect a "temporary" cure—I use the word *temporary* advisedly—we must have resort to saturated solutions of **nitrate of silver** or even the solid nitrate itself. If rubbing a tiny scrap of the **ointment of the yellow oxide of mercury** [1 grain to 1 dram (0.065 to 4 Gm.) of vaselin] upon the well-washed and thoroughly dried edges of the eyelid and into and in and around the cilia does not effect a cure, we must have resort to the nitrate of silver locally, brushing a strong solution carefully upon the edges of the lids and around the cilia or actually with a fine point of the solid caustic cauterizing the ulcerated area around the openings through which the cilia project.

In all but the oldest cases the application of **protargol** after the manner recommended by Darier is capable of bringing about a rapid cure. The scrubbing with protargol not only loosens the crusts, but also insures that the silver reaches the diseased tissues at the bottom of the hair-follicles. When the disease is of very old standing, so that the roots of the hairs are already atrophied, the thickened edge of the lid is everted, and there is troublesome lachrymation, for which the sufferers seek relief in one clinic after another

without finding cure. In such cases good results follow the application of compresses wetted with **ichthyol** during the night. The good effects, however, are partly lost on account of the very considerable pain which followed the application. Reumaux (La Clinique ophthal., May 10, 1904).

A good **cleansing** given by the **surgeon** himself, and a final light swabbing with a weak solution of **silver nitrate**, will do more than gallons of lotion liberally bestowed during many weeks. Then the application of a smooth antiseptic ointment will keep the lids soft and reduce the liability to the collection of more crusts and scabs. Plain **boric ointment** in yellow vaselin, or a doubly diluted **ointment of ammoniated mercury**, or the **yellow oxide of mercury** in a mixture of lanolin and vaselin to the strength of 1 per cent., are all of value, the last perhaps most of all. These measures will do much to reduce the unsightly ravages made by the disease, but they will not touch the thing which is most frequently the real cause of the irritation. To get at this the refraction of the eye must be made out, by retinoscopy, and any irregularity found must be corrected with glasses. N. B. Harman (Clin. Jour., Sept. 19, 1906).

The crusts are usually quite adherent, owing to their composition, partly to the sticky secretion of the Meibomian follicles, and partly to a varnish-like substance (serum) which exudes from the hair-follicles. A weak **solution of sodium bicarbonate** softens and detaches them.

As we have said, it is but "temporarily cured." Unless the cause of a blepharitis be removed, it will return. We have treated the local condition and not removed the cause. This, in our experience, is due, in the majority of cases, to a refraction error (usually hyperopia), and is simply an expression of functional

strain. A careful refraction worked out under full atropine mydriasis, or by the rapid method when the patient is over 45 years of age, is the best treatment for the simple reflex and ordinary form of blepharitis that an experience of more than a quarter of a century now suggests.

Blepharitis ciliaris (eczematous) occurs as a concomitant of eczema, seborrhea, and other skin affections, and as a complication of vaccinia, syphilis, and other infectious processes, or may be parasitic, and is to be treated according to the rules of therapy in dermatology. *Pediculi palpebrarum* usually transferred from the pubic region securely tucked between the eyelashes looks like a lid with a double row of cilia and readily yields to applications of **mercurial ointment**.

The writer has obtained excellent results in the treatment of blepharitis ciliaris by the application of the following ointment:—

I.

℞ *Salicylic acid* .. gr. ivss (0.3 Gm.).
Zinc oxide gr. xv (1 Gm.).
Wool fat,
Petrolatum,
 of each gr. lxxv (5 Gm.).
 M. et ft. ungt.
 Sig.: For external use.

II.

℞ *Tumenol* gr. ivss (0.3 Gm.).
Zinc oxide gr. xv (1 Gm.).
Petrolatum,
Wool fat,
 of each gr. lxxv (5 Gm.).
 M. et ft. ungt.
 Sig.: For external use.

The two ointments are applied at night, every second day. If suppuration ensues, the lashes should be plucked out and the parts cauterized with silver nitrate. Pick (*Therap. Monats.*, April, 1910).

Blepharitis ciliaris (furunculous) is a variety peculiar to no local or reflex

condition, but is caused, as a rule, by an infection. Such inflammations follow the usual course of furuncular inflammations and abscesses, and the secretion from the localized slough furnishes the typical "furuncle bacillus." For this reason alone the boils, or furuncles, not necessarily "styes," recur, and acute autoinfection through the mouths of the Meibomian follicles occur and recur. Unless severe antiseptic precautions are rigidly enforced, particularly when the abscess contents are evacuated, such are sure to recur. **Hot fomentations** with boiled water, followed by drenchings with **borated** or any **mild antiseptic solution**, are absolutely necessary.

The writer advises ichthyol in various combinations:—

℞ *Ichthyol* gr. vj (0.39 Gm.).
Petrolatum ʒij (8 Gm.).

M. et ft. ungt.

Sig.: Apply to the edges of the lids after cleansing.

℞ *Ichthyol* gr. x (0.65 Gm.).
Zinc oxide ointment ʒij (8 Gm.).

M. et ft. ungt.

Sig.: Apply to lids after removal of crusts.

Lead acetate should not be employed in connection with the eye, as it has the defect of depositing an insoluble salt upon any corneal abrasion, making a stain that cannot be removed. Lead and opium wash, so frequently used in other parts of the body, is not, therefore, a desirable application to the eye. May (*N. Y. Med. Jour.*, Sept. 9, 1911).

When furunculous abscesses are evacuated spontaneously or by the knife, a focus of infection is established, and we must use dilute **listerine**, **Dobell's solution**, **Seiler's solution** (tablets), **electrozone**, or **dioxide of hydrogen**, until complete

healing has taken place. Fomentations are best made while the patient reclines. Squares of **spongiopilin** or pledgets of absorbent cotton covered with oil-silk are most convenient. Following hot fomentations, the eye should be lightly covered and protected from draughts.

Loss of cilia, even in part, caused by destruction of glands is seldom seen, but to be deplored, as such loss of cilia robs the eye of its protection against light. Cilia generally grow again unless the edges of the lids are sclerosed and deformed with cicatrices from any cause, usually neglected ulcerations about the mouths of the hair-follicles.

Closure of the puncta lacrymalia is the most serious complication. All careful operators take great pains to **cleanse the cilia**, especially the superior ones in any case. It is unsafe to operate with blepharitis present, as the secretions would infect the wound. Such are known as "dirty eyes."

The following routine prescription for cases of narrowing of the tear-ducts is an especial favorite with young people, who often are anxious to suddenly do away with red eyelids and at the same time be able to use an antiseptic bleaching solution, which can be used with impunity, but never replenished without another prescription. Of course, the cocaine, for evident reasons, may be omitted, but it is of value, as it prolongs the effect of the adrenalin:—

℞ *Boric acid powder* gr. x (0.65 Gm.).
Cocaine muriate (2%
solution) 3j (4 Gm.).
Solution adrenalin
chloride (1:1000),
Water of each 3ij (8 Gm.).

Sig.: Put one drop into either eye before and after each meal, or oftener.

In *phlegmonous*, or *erysipelatous*, *blepharitis ciliaris* with abscesses of the upper lids, and in all cases of ecchymosis or other swellings, great care should be exercised. Such should be evacuated if possible while a horn spatula separates the lids and the eye lest the eyeball be cut into.

A fact worth noting is that blepharitis ciliaris is seldom found accompanying myopia.

If blepharitis ciliaris is a symptom of functional strain of reflex eye origin, headaches are seldom present. If, on the contrary, headaches are the one symptom, blepharitis, or blepharadenitis, is generally conspicuous by its absence.

If one eye be used more than the other, or if one eye be not used at all, more or less blepharitis ciliaris will likely indicate the amount of strain.

Scabies of the palpebral fissure is not a commonly recognized condition. The writer, however, describes this form of scabies. The acarus seems to affect the ciliary follicles and may thus escape detection. There is considerable blepharitis, accompanied by itching and tingling, along the free border of the eyelids. The eyelashes fall out. There is hyperemia of the inner marginal zone and of the neighboring skin. A honey-like secretion covers the border of the eyelids and adheres specially to the point of emergence of the eyelids. There is often a considerable degree of conjunctivitis. The treatment recommended consists in applying an ointment of **Peruvian balsam** 2 parts, **lanolin** 6 parts; or **Peruvian balsam** 2 parts, **lanolin** 4 parts, **oil of sweet almonds** 2 parts. This must be applied every day, and left on for about half an hour. The condition may be cured in four or five days, but the applications ought to be continued for some time. Raehlmann (*Jour. de méd.*, Feb. 10, 1900).

The following ointment has been used by the writer with remarkable success:—

℞ *Copper sulphate*,
Ichthyol .of each 8 grs. (0.5 Gm.).
White vaselin ... 1 oz. (30 Gm.).

It does not affect the cornea or the conjunctiva, and so uniform were the results that it might be considered a specific in blepharitis. It is useful in all forms of the affection as preferable to any other application that has ever been used. The ichthyol acts as an antiseptic and a stimulant, while the copper sulphate exerts astringent properties, reducing the congested sebaceous glands of the eyelids. Ráimondo Ferro (Gazz. d. Ospedali, March 2, 1902).

In the cases in which the alopecia of blepharitis marginalis is present without ulceration or apparent desquamating conditions, or such as may be due to parasitic or microphytic causes, in persons who have neither syphilis nor leprosy, the application of **phenol** often produces brilliant results. The writer has never seen hair restored in palpebral alopecia in a subject of general alopecia. In syphilitic subjects, where the hair has fallen from the brow, eyelids, and head, all efforts at restoring it to the lids by local applications have failed in the writer's hands, nor has he seen the lash reappear in syphilitic cases under any form of constitutional treatment. D. S. Reynolds (N. Y. Med. Jour., June 6, 1903).

Blepharadenitis is only an aggravated subacute or chronic form of blepharitis ciliaris, in which the mouths of the Meibomian follicles have become closed and the lining membrane of the glands has become subacutely or chronically inflamed. Retention cysts and abscesses with pyogenic membranes secrete pus from granulating sacs and deform the lid.

Unless every particle of **diseased gland** with its pyogenic membrane be carefully removed, recurrence will

take place, and careless removal (enucleation) means injury to the tarsal cartilages: needless to say, will cause deformity. Epiphora, entropium, and ectropium will ensue, and with them what is best described as "wrinkled lid" will remain as a permanent source of trouble, and rub its irregular surfaces over a cornea doomed to destruction from irritation and deposit of connective-tissue macules of the cornea or pannus.

Persistent epiphora and localized swelling in the course of the tear-duct, with more or less interference with drainage and a subacute conjunctivitis, must be suspected as possibly being caused by lachrymal calculi (leptothrix), which are only removed by slitting the duct. Such rare formations are light brown in color and of a waxy consistence.

We can recall the time spent years ago in fighting blepharitis and blepharadenitis before its true cause was recognized and understood. At present, and in the light of modern ophthalmic surgery, we recognize in blepharitis, or blepharadenitis, as we have said, only a symptom which in a general way promptly yields to prophylactic treatment. The elimination of the latter as promptly brings relief in other directions: not only by improving the personal appearance and the vision, but also by curing lifelong headaches and other neuroses.

Errors of refraction are sometimes responsible for the onset of the disease, by inducing hyperemia, which spreads through the conjunctivæ to the lid margins. It is, therefore, important to prescribe any correcting glasses that may be required. Arnold Lawson (Practitioner, Oct., 1911).

CHARLES S. TURNBULL,
 Philadelphia.

BLOOD-PRESSURE.—By blood-pressure is meant the arterial tension or pressure of the blood in the vessels within which it is contained.

High blood-pressure appears to depend chiefly on a narrowing of the lumina of the arterioles in the pre-capillary areas. It is at first functional and caused by hypertonus of the arterial musculature, though later it assumes a partly organic character. The different types of chronic arterial hypertension probably represent different stages in the development of the same fundamental process, which may advance with variable rapidity and with variable associated involvements of cardiovascular, renal, cerebral and other structures in different cases. When recognized early, the process may often be arrested or so delayed in its progress that patients may live comfortably for many years before troublesome symptoms or dangerous complications occur. L. F. Barker (*Trans. Ohio State Med. Assoc.; Jour. Amer. Med. Assoc.*, July 24, 1920).

SYSTOLIC AND DIASTOLIC.—

Blood-pressure is divided into the maximum or systolic pressure and the minimum or diastolic. The systolic is the greatest pressure exerted, and takes place during systole of the heart; the diastolic is the lowest pressure, and occurs in the cardiac cycle just at the beginning of systole, or at the end of diastole, the time when most of the blood has passed on through the capillaries into the veins.

PULSE-PRESSURE.—From these we obtain "pulse-pressure," which is the difference between the diastolic and the systolic; and also the mean pressure, which is about the average between the systolic and the diastolic readings, but has little clinical value and is seldom used.

The Importance of Blood-pressure and Conditions to which it Applies.—

The whole subject is one which has become prominent from a practical standpoint, in this country, in about the last eleven years, though it had its beginnings as far back as 1828 in Europe.

It has been, however, only in the last ten years that the importance of accurate blood-pressure readings in their diagnostic, prognostic, and therapeutic application to general medicine have begun to be appreciated, and their value realized by the general practitioner.

Blood-pressure determinations are now of so well-recognized value in medicine and surgery that one of the important questions of today is, What is their application and meaning in special conditions, and how reliable are they when other means fail us?

Theo. C. Janeway with great clarity expressed the matter in one of his articles, "When Should the General Practitioner Measure Blood-pressure?"

He said in substance: 1. It should be taken in the first examination of every patient. 2. Occasionally for watching the progress of cardiovascular disease and nephritis. 3. Examination for certifying to the state of health in: life insurance; applicants for the army, navy, police, fire department, and in schoolboys engaged in athletics; and he also mentions eclampsia and diagnosis in conditions with abdominal pain.

In addition the work of Briggs and Cook has shown blood-pressure determinations to be one of the most important aids in diagnosis and treatment of eclampsia and cardiorenal disease, and its undoubted value in typhoid fever medication in children;

in surgery before, during, and after operative procedures, and injuries of the head, etc.

In life-insurance examination almost all companies now recognize blood-pressure estimation as a necessary procedure. The reason for this is very clearly shown in the statistics from the Northwestern Life Insurance Company, which was one of the pioneers in taking blood-pressure readings on its applicants. In a letter to their examiners they say: "The statistics on 1247 cases at all ages, in which there was a blood-pressure of 150 mm. mercury and over, show a mortality two and one-half times greater than the general average mortality of the company covering the same period. In 891 of these cases there was no other impairment recorded in the application when received at the home office. All these risks would have been granted insurance had not blood-pressure been taken. A careful study of the statistics of this company demonstrates, without a doubt, that the use of the sphygmomanometer is indispensable in our examination for life insurance. The statistics also demonstrate, in our opinion, that the use of the sphygmomanometer will be of equal value to the practitioner in his general practice, and that no physician should be without this valuable aid in diagnosis."

Blood-pressure determinations are of value also to specialists in eye and ear conditions; in fact, there is no branch of medicine in which blood-pressure is not significant, and often an aid when other means of diagnosis have not been sufficient.

HISTORICAL.—Going a little into the history of blood-pressure

determinations we find it dates back to 1828, when Poiseuille introduced the first U-tube mercurial manometer.

Shortly afterward Ludwig devised the kymographion, a manometer connected directly to an open artery, and recording on a revolving cylinder; but it was not until 1876 that a useful apparatus for estimating blood-pressure in man was used by Marey, by which he could determine both systolic and diastolic blood-pressure.

There was, however, no general use of blood-pressure apparatus until some eleven years later (1887), when v. Bosch brought forward his apparatus, consisting of a small rubber bulb filled with water connected with a mercurial manometer; the bulb being pressed upon the radial artery until the pulse was just obliterated, and the pressure read off the manometer. V. Bosch later modified his apparatus by using an anaëroid in place of the mercurial manometer.

V. Potain further substituted on the v. Bosch apparatus air in place of water, which was a great advance, but both instruments have a large possible error which Tigerstedt claims has reached 78 mm.

All our modern apparatus dates from 1896, when Riva-Rocci, in Italy, used a rubber bag, 5 cm. wide, surrounded by an inelastic material, and completely encircling the arm. This cuff was connected, by rubber tubing, with a reservoir of mercury having an upright capillary tube, alongside of which was a mm. scale. Air was pumped into the cuff, compressing the brachial artery until the pulse below the band was obliterated, and then, by releasing the air slowly, he determined when the pulse reappeared, and thus obtained a reading

of the maximum or systolic pressure, shown by the column of mercury in the capillary tube.

All instruments which give accurate readings have utilized the principle of the pneumatic constricting band, except that now the width of the cuff is at least 12 cm., as the narrow cuffs, such as the original Riva-Rocci, give too high readings. This very important error was shown by the work of v. Recklinghausen to be due to the loss of pressure in compressing the tissues, and that it could be eliminated if a cuff from 12 to 15 cm. wide were utilized. Theo. C. Janeway stated that he had found in high-tension cases a 5-cm. cuff to register as much as 60 mm. higher than a 12-cm. cuff.

All our modern blood-pressure determinations, as on the Riva-Rocci instrument, are recorded as the pressure measured by the height of a column of mercury of so many mm., or, in other words, mercury is the standard on which blood-pressure readings depend.

METHODS OF MEASURING BLOOD-PRESSURE.—As all accurate modern instruments for estimating blood-pressure utilize the pneumatic principle of the Riva-Rocci, the methods of blood-pressure determinations are about the same, as follows: The apparatus used being set up ready to operate, the pneumatic cuff is adjusted snugly, and without compression, to either the thigh or the arm, usually the arm, taking care that the cuff is at the level of the heart. The cuff is then inflated until the pulse below the constriction is obliterated, which is determined by palpating the artery. The estimation of blood-pressure is

then made by either one of two methods: 1. The old, or palpation, method. 2. The new, or auscultation, method, described in 1906 by Korotkoff.

PALPATION METHOD.—(a) **Systolic.**—After obliterating the arterial pulsation in the vessel below the cuff, slowly release the air-pressure, allowing the mercury to fall evenly, and note the height of the column when the pulsation reappears to the palpating finger. This gives the systolic or maximum pressure, and will be found easy to obtain on all instruments.

The most satisfactory and probably the most trustworthy determination of the systolic pressure is by the palpatory method, while for the diastolic pressure either the change of sound or the disappearance of all sound should be taken as the criterion, depending upon the accuracy of the determination in each individual case. The point selected should be recorded and always used in the future work with the same case. The systolic pressure is unquestionably of much more value than the diastolic and, contrary to general opinions, the relative range of variation in the normal subject is wider in the diastolic than the systolic. The pulse pressure is subject to still greater variations, and several factors beside the volume of blood ejected from the heart influence it, *e.g.*, vasoconstriction and dilatation, either generalized or local. The systolic pressure is certainly of value in arterial and renal diseases, cerebral pressure, the toxemias of pregnancy, Addison's disease, and to a less extent in the diagnosis of aortic insufficiency.

A very valuable use is in the early discovery of *pulsus alternans*, which can often be brought out by careful adjustment of the cuff pressure so as to cut out every alternate feeble beat, even where the alteration is not otherwise appreciable by

the finger. E. S. Kilgore (*Lancet*, Aug. 24, 1918).

(b) **Diastolic.**—1. After taking the systolic pressure allow the mercury to fall slowly, and note the varying degrees of oscillation of the mercury column. Read the scale at the base of the maximum fluctuation and it gives the diastolic pressure. 2. Or when the first change from a small to a full, bounding pulse is noted, read the height of the mercury column, and it gives the diastolic pressure.

Considerable stress has been laid by many writers upon the importance of diastolic pressure in addition to the systolic and the pulse-pressure. L. F. Mackenzie (*Med. Rec.*, Dec. 18, 1915) refers to it in fact as the fundamental pressure upon which blood-pressure readings should be based. It is much less influenced by emotions than the systolic; measuring as it does the peripheral resistance, it is the pressure which the heart must first overcome, and which imposes constant strain upon the aorta and aortic valves.

The diastolic pressure is more constant for any individual than the systolic pressure. Furthermore, it is probably a more accurate index of high or low tension than the systolic pressure because, as stated, it measures the amount of peripheral resistance. Moreover, it is very necessary accurately to determine the diastolic blood-pressure, because the pulse-pressure can thus be obtained by subtracting the diastolic blood-pressure from the systolic. The pulse-pressure, thus determined, represents the actual head of pressure which is forcing the blood to the periphery; the efficiency of the heart action in the face of the existing state of peripheral resistance. A study of these three landmarks in blood-pressure reading gives us desired information concerning the circulation in both the heart and peripheral blood-vessels; the therapeutic importance is plain. Warfield (*Illinois Med. Jour.*, in *N. Y. Med. Jour.*, May 29, 1915).

The formula of the normal relation of the systolic, the diastolic, and the pulse-pressure is 3:2:1, for example, systolic 124, diastolic 82, pulse-pressure 42. Faught (*Med. Record*, Mar. 10, 1917).

AUSCULTATION METHOD.—(a) **Systolic.**—As in the palpation method, having inflated the cuff until the pulse is obliterated, place the bell of an ordinary binaural stethoscope over the artery just below the cuff. Now release the air-pressure slowly, and listen with the stethoscope. When the first cardiac beat passes the constricting cuff a loud, clear thump is heard, and the true systolic pressure is obtained by reading the height of the mercury column.

The writer considers systolic readings as relatively worthless for diagnostic purposes. The most important information is given by the pulse-pressure, or the difference between the systolic and diastolic readings. A falling pulse-pressure is measurable and gives the earliest indication that a patient is not doing well; a rising pulse-pressure points to favorable progress. J. J. Rowan (*Jour. Amer. Med. Assoc.*, Mar. 18, 1916).

(b) **Diastolic.**—In taking the diastolic continue to release the air-pressure and listen over the artery. The thumping sound is followed by a murmur, and then by a second thumping sound which becomes fainter and suddenly disappears. At the time of the disappearance of all sound, again note the height of the mercury column, which gives the true diastolic pressure.

This last auscultation method has almost revolutionized the determination of blood-pressure, for diastolic pressure can be as easily and accurately determined as systolic pressure,

a result impossible to attain in the past, there being such a large personal element in obtaining the diastolic pressure that most observers did not attempt it.

The diastolic and pulse pressure (difference between systolic and diastolic) are thus accurately determined by this method, and are often of even greater importance than the systolic.

Experiments on dogs showed that whereas the pulse-pressure in the larger arteries (femoral) varies extensively, it varies within narrow limits only in the small ones (dorsal artery of the foot). These results supply an experimental explanation for the fact that in man uniform pressure readings were obtained by Gaertner's method at the digital artery. Cohn and Lundsgaard (*Jour. Exper. Med.*, Apr., 1918).

Here I wish to make clear a point which has created considerable confusion in the past, the relation of the inertia of the mercury column to the determination of the diastolic pressure, and also as to whether it is of importance for the column of mercury to fluctuate with each pulsation of the heart. Were we to adhere to the old method of reading the diastolic pressure the mercurial inertia might be of slight importance, but from a practical standpoint of little significance.

When we use the auscultation method for determining diastolic readings, a method now almost universally used, on account of its ease and accuracy, the lack of fluctuation of the mercury has absolutely no disadvantage. On the contrary, it becomes easier to obtain the true pressure reading, where the column is not actively oscillating, as is the needle of an anaëroid. Blood-pressure determination is a question of the pressure

existent in the arterial system, not of the pulsation of the heart.

The studies of Warfield and others have shown the clinical importance of the diastolic test. It can be relied upon to give a correct reading under practically all circumstances, irrespective of the age of the patient, the character of the vessel, or the size of the arm to which the cuff is attached. We fail to obtain the best from our sphygmomanometer if we omit the diastolic observation. Moreover, in many conditions, of the two blood-pressure tests, the diastolic, which can be just as accurately made, is often more valuable than the systolic. F. A. Faught (*Interstate Med. Jour.*, Aug., 1914).

In the **auscultation method** it is largely a question of the physics of fluids, *e.g.*, the artery is constricted by means of the pneumatic cuff; below it there is no arterial flow, and the vessel walls are in a semirelaxed condition. The blood-pressure is lowered in the cuff gradually until the heart has power enough to drive some blood into the relaxed vessel beyond. The sudden flow of blood into the relaxed vessel sends the wall into vibration, and a loud, clear thump is heard which gives the systolic pressure. In making the diastolic estimation there is again a physical condition of a fully expanded artery above the pneumatic cuff, a constriction under the cuff, and an enlargement below. Fluid passing from a large tube through a constriction into a large opening makes a murmur, exactly what takes place, and when the caliber of the tube is uniform, or, in other words, when the diastolic pressure is able to overcome the constriction of the cuff, there will be no longer any sound. It can easily be seen that it makes no difference

whether the mercury column records each pulsation of the heart or not, but that it shows much more easily and accurately the correct blood-pressure than could be read if it were fluctuating very actively.

C. F. Judson and Percival Nicholson (See N. Y. Med. Jour., July 4, 1914) made 2300 blood-pressure observations upon **children** whose ages ranged from 1 to 14 years. We found the auscultatory method superior to the palpation method, and the modification of the Erlanger apparatus to be the best. The gradual increase in the blood-pressure takes place up to 13 years of age. From 10 to 14 years, at puberty, there is a rapid increase in pressure, owing to the great increase in the size of the heart at that time. The variation from four years to puberty is less than 8 mm. and the total rise from 4 to 14 years of age is 14 mm. The systolic pressure as of more importance than even the diastolic or pulse-pressure, although in certain heart lesions the diastolic pressure is extremely important in establishing the prognosis.

In **children**, estimated by the auditory method which the writers consider simple and determinate, the average systolic pressure is 108.1, the average diastolic pressure 72.4, and the average pulse-pressure 35.7 mm. mercury. The cardiac output is small in them; besides, the capillary system to be filled is very limited as compared with the adult. Yet the systolic pressure is only slightly lower in children than in adults. The average diastolic level, on the other hand, is decidedly higher in children than in adults; this is the main cause of the considerably smaller pulse-pressure in children—35.7 mm.—as compared with 46 mm. in adults. By the tactile method the average systolic pressure was 105.7 in children as compared with 108.7

in adults, while the range was 125-84 in the former and 132-92 in the latter. By the auditory method the range of systolic pressure was 130-90 in children and 135-92 in adults, while the range of diastolic pressure was 90-50 in the former as compared with 82-50 in the latter. In children the relation of pulse-pressure to systolic pressure was 1:3 and to diastolic pressure 1:2, while in adults this relation was 1:2.7 and 1:1.6 respectively. Melvin and Murray (Brit. Med. Jour., Apr. 17, 1915).

In the **aged**, 100 women and 50 men examined by the writer, the systolic and pulse-pressure increased to the age of 85 and then decreased. The diastolic pressure did not vary much after the age of 70. The blood-pressure was higher in women except after the age of 90. There were a few who had very high blood-pressure without symptoms. They were going about their everyday duties in apparently perfect health. Bowes (Jour. of Labor. and Clin. Med., Jan., 1917).

The beginning of regular, rhythmic snapping sounds is the best criterion point for use in measuring the systolic pressure. The criterion for measuring the diastolic pressure is the lowest point where the snapping sounds are heard, or where they just cease. The auditory method of measuring blood-pressure is more satisfactory than the palpatory or sphygmographic methods. Brooks and Bleile (Jour. Amer. Med. Assoc., Aug. 17, 1918).

CHOICE OF AN INSTRUMENT.—

The number of instruments at present available for blood-pressure work is legion, and it is decidedly confusing, to one entering this field, to select a good practical instrument.

In his book, "A Clinical Study of Blood-pressure," Theo. C. Janeway gives the following advice, on the choice of a sphygmomanometer:—

"1. Manometer must be of such

construction as to give permanently exact readings. No metal manometer yet invented remains accurate; hence, this means the use of a properly graduated mercurial one.

"2. Compressing armlet must have a width of at least 12 cm.

"3. Connections must be practically non-distensible tubing.

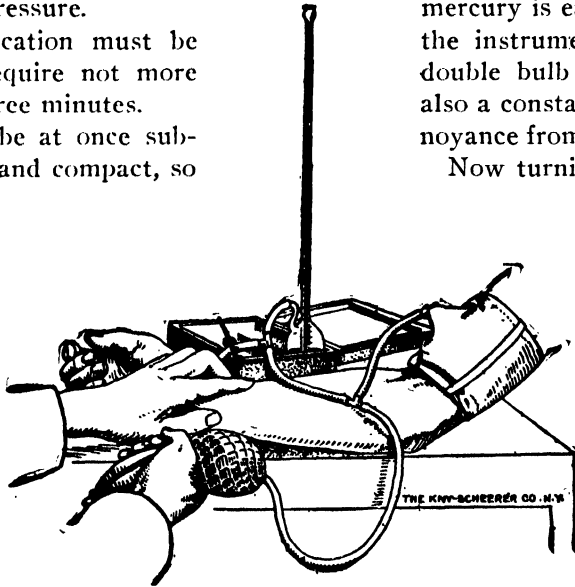
"4. It must measure both systolic and diastolic pressure.

"5. Its application must be simple, and require not more than two to three minutes.

"6. It must be at once substantial, light, and compact, so

be filled with air until the pulse at the wrist is just obliterated. This is a fairly accurate instrument for determining systolic readings, but, not having a good air release, is not practical in determining diastolic pressures. It is inaccurate in that it uses a 5-cm. cuff, which gives too high readings. Though by the use of a jointed tube it is fairly compact, the mercury is easily spilled and the instrument fragile. Its double bulb for inflation is also a constant source of annoyance from blowouts.

Now turning to cut No. 2



1. Cook's sphygmomanometer.

that it may be easily and safely carried.

"7. It must not be too costly."

Instruments.—As it is impossible to describe all the forms of apparatus, a few of the simpler and more practical instruments may be mentioned. The simplest mercurial instrument is the Cook modification of the Riva-Rocci. (See cut No. 1.) It utilizes all the principles of the original Riva-Rocci instrument, consisting of a constricting pneumatic cuff connected with a mercurial manometer, and having a means of inflation. The cuff when applied over the brachial can

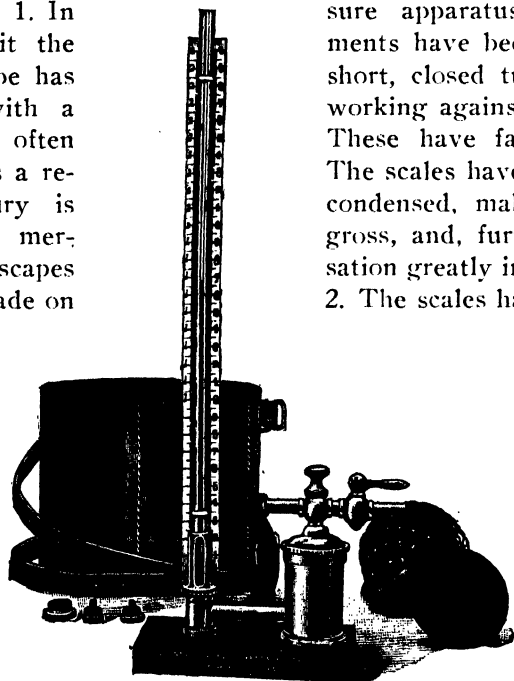
the original Stanton apparatus is seen, a reliable instrument, but no longer manufactured. It was a large, heavy instrument having several defects, as:

1. The use of a 10-cm. cuff, which gave too high readings.
2. It was not very portable, requiring to be taken apart and set up when used in general practice.
3. It was difficult to prevent the mercury from escaping.
4. It had the same defect as the Cook apparatus in that it used a double rubber bulb for inflation. However, it was largely adopted and gave accurate readings when a wide cuff was used.

Cut No. 3 shows the Janeway apparatus, a more portable instrument devised by Theo. C. Janeway. This instrument has the advantage over the others named above, in that it used an accurate 12-cm. cuff, and hence the readings were correct on most of the instruments. But it also has its defects: 1. In order to carry it the end of the U-tube has to be closed with a cork, which is often forgotten and, as a result, the mercury is spilled. 2. The mercury often escapes from the joint made on

found to vary 40 mm. 5. The rubber tubing comes in direct contact with the mercury, and sulphide of mercury is formed, coating the glass black and causing friction, with inaccurate readings.

In order to attain portability, a greatly desired feature in blood-pressure apparatus, several instruments have been made having a short, closed tube with mercury working against the inclosed air. These have failed because: 1. The scales have necessarily to be condensed, making the readings gross, and, further, this condensation greatly increases any error. 2. The scales have to be specially



2. Stanton's sphygmomanometer.

the long arm of the U-tube. 3. As made now, there is a wide metal union which obstructs the reading for some 30 mm. in the middle of the scale. 4. Like all U-tube instruments, it utilizes a scale condensed one-half to allow for the descent of one column while the other rises. This might be accurate were it not impossible to obtain glass tubing of uniform caliber; consequently, there is often an inaccuracy, one column being balanced against the other, and therefore any error is multiplied by two. Two instruments recently examined were

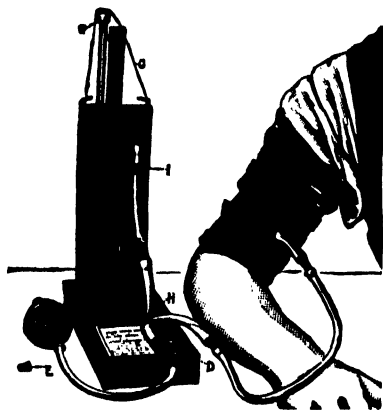
standardized by comparison with a mercurial column, and, being fixed on the glass, cannot be adjusted to allow for any change in the compressibility of the inclosed air column, which varies greatly according to moisture, temperature, and climate.

In addition, there are the anaëroids, or spring diaphragm instruments, following the old model of v. Bosch. These, while convenient in some respects, as Janeway says, "need to be standardized frequently by comparison with a mercurial manometer, which is irksome, and they are diffi-

cult of repair. Depending as they do on a spring, they wear out and are not dependable."

Finding the need for a reliable, accurate, durable, simple, portable, and inexpensive mercurial apparatus, the author has added one more to what might seem an already well-filled field.

The instrument shown in cut No. 4 is simply a short form of mercurial instrument, utilizing the open tube, and so arranged that the mercury needs no pouring and cannot be



3. Jaueway's sphygmomanometer.

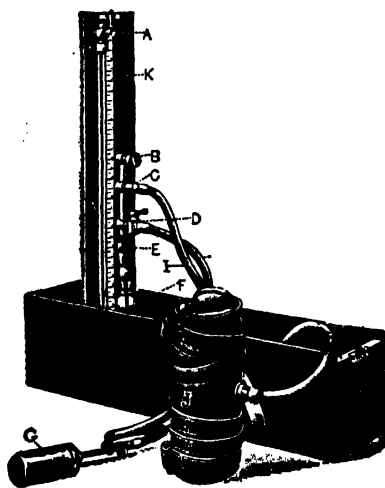
spilled. By the use of a steel stop-cock and flint glass there is no corrosion of the mercury. The instrument is only 13½ inches long, and when closed will fit in the ordinary doctor's bag. Accuracy is maintained by the use of a scale adjustable to the mercury level, allowing for changes of climate and temperature, and by the use of a wide, easily adjusted, soft cuff (14 cm.) (cut shows old type of rigid cuff). The air-pressure is easily and steadily released by means of a needle-valve.

There are several forms of accurate instruments, but owing to their expense and size they are not avail-

able in general practice, *e.g.*, the Erlanger, etc.

THE BASIS OF BLOOD-PRESSURE.—In order to utilize blood-pressure determinations, and make them of real value, it is necessary to understand on what they depend, as well as what physiological factors are involved, and variations possible without pathological changes.

While from a theoretical standpoint there are a large number of physio-



4. Nicholson's sphygmomanometer.

logical factors to be considered, many of these do not, from a clinical standpoint, influence blood-pressure determinations to any great degree.

Blood-pressure depends on four main factors: 1. Cardiac strength. 2. Peripheral resistance in the vessels. 3. The elasticity of the vessel walls. 4. The volume of blood. Besides these there are several other factors, but they are not of great clinical importance, *e.g.*, viscosity of the blood, etc.

The heart during systole, shortly after the beginning of its contraction, drives the blood out into the aorta. The pressure in the aorta then

reaches the maximum, and shortly after the aortic valves close. The pressure from then on until the next systole is maintained by the elasticity of the vascular walls, and as the blood is being forced on through the capillaries the pressure gradually falls and reaches its minimum at the end of diastole.

The pressure depends mainly on the contractile power of the heart and the peripheral resistance which it has to overcome. The peripheral resistance depends on the degree of contraction or caliber of the vascular walls, and also on their distensibility.

The caliber of the vascular walls in turn depends on the vasomotor center, the balance between vasoconstriction and vasodilation, and its close interaction with the heart through its nerve supply.

As can be easily seen, the maximum or systolic pressure approximates the intraventricular pressure, while the minimal or diastolic pressure represents the peripheral resistance. The pulse-pressure, or difference between the two, represents the head pressure driving the blood on out through the arterioles, *e.g.*:—

Systolic, or maximum	150 mm. Hg.
Diastolic, or minimum	120 " "
Pulse-pressure	30 " "

The point to be especially emphasized is that the maximum or systolic pressure by itself indicates mainly heart strength, but equally, if not more, important the peripheral resistance is shown by the minimum or diastolic pressure, and the head of flow is shown by the pulse-pressure.

In the past very little work has been done on diastolic pressure and pulse-pressure, a fact due largely to

the difficulty in obtaining reliable readings with the instruments available and the methods used, but this is no longer the case where the auscultatory method, already described, is utilized.

Discussion of Pulse-pressure and Diastolic Pressure.—Before going farther it might be well to consider pulse-pressure (*the difference between systolic and diastolic readings*) and diastolic pressure more in detail.

Various figures have been given for the normal range of pulse-pressure:—

Erlanger	30 to 45 mm. Hg.
Hirschfelder	30 to 40 " "
Young	25 to 30 " "

Lauder Brunton says: "Diastolic pressure is to the systolic pressure, under normal conditions, as 3 is to 4." This gives the pulse-pressure as one-fourth of the systolic reading.

He further states: "Diastolic pressure has as yet received comparatively little attention because of the difficulty of ascertaining it, yet it is a factor of great importance because by its amount and by the difference between it and the systolic pressure we obtain valuable data in regard to the strength of the heart and condition of the arterioles."

In substance he also gives the following:—

Pulse-pressure depends on the pulse-rate. If the pulse is slowed more time is allowed for the blood to run through the arterial system during diastole. Diastolic pressure will be lowered and pulse-pressure increased. The reverse also applies.

A weak heart will not raise tension as rapidly as a strong one, and the time between the end of each systole and the next will be shorter and the pulse-pressure lower. In a stronger

heart the interval between systoles is longer and there is a larger pulse-pressure.

Now, turning to the blood-vessels, we find when contracting the diastolic pressure remains high, giving a small pulse-pressure, and *vice versa*.

A low systolic pressure with a large pulse-pressure shows dilated vessels and a probably strong heart.

Normal Readings.—Before turning to the consideration of blood-pressure under abnormal conditions, let us consider the normal variations that have been determined by numerous observers. It is well to bear in mind the fact that blood-pressure standards cannot be absolutely fixed, being of considerable variation in different healthy individuals:—

	Age.	Systolic.	Diastolic.	
Erlanger	19 to 25 years	110	65 mm.	Hg.
Hirschfelder	All ages	115-120	75-85	"
Janeway	Before middle life	100-130	25-40 mm.	} lower than systolic.
	After middle life	130-145	25-40 "	
	Children before 2d year	75-90		
	Children after 2d year	90-110		
<i>Abnormal.</i>			Systolic.	
	Before middle life, pressure above	145	mm.	Hg.
	After middle life, pressure above	160		
<i>Normal.</i>				
Cook	Before 30 years	120-130	"	"
	30 years on	125-140	"	"
<i>Low limit.</i>				
Janeway	Male	100	"	"
	Female	90	"	"

A low systolic pressure with a slight pulse-pressure indicates the heart itself is weak; in addition, there is probably some dilatation of the vessels, though a feeble heart with normal vessels could give these signs.

If there is a high systolic pressure and a correspondingly high diastolic pressure, giving a normal pulse-pressure, we may assume there is a normal balance between heart and vessels, and a compensatory condition is present.

Thus pulse-pressure is of the greatest value in determining the condition present, whether mainly due to heart or arteries, and is most important in relation to treatment. By observing the changes in pulse-pressure of our cases under treatment we obtain the most accurate idea possible of the results that are being attained; far more so than when we utilize the systolic pressure alone.

In general it may be stated that females are about 10 mm. lower than males. The lowest blood-pressure readings according to Hensen were 40 mm. systolic, and lowest possible pressure with recovery was approximately 55 mm. Cook and Briggs consider 60 mm. systolic severe. Janeway, pressure below 75 mm. systolic rare except during operation, when it has reached 40 mm. The lower limit represents the resistance of the arterioles, due to the necessary vasomotor tone, and is probably never less than 50 mm. mercury.

PHYSIOLOGICAL VARIATIONS IN BLOOD-PRESSURE.—

Where there are no pathological changes, the following factors affecting blood-pressure are to be taken into account:—

Location of Cuff.—It is important that the constricting cuff shall be on a level with the heart; other-

wise, the correct reading is lowered or raised by the effect of gravity on the column of blood according to whether the constriction is above or below the heart level. If above, the readings will be too low; if below, they will be too high.

Position of Patient.—The position of patient in relation to the horizontal is also important, systolic pressure being 8 to 10 mm. higher in the reclining than in the sitting posture.

There is about the same difference between sitting and standing posture. The diastolic pressure also rises but relatively higher than the systolic, and as a result pulse-pressure is decreased. The pulse-rate is also increased. The main point is, therefore, to always take subsequent readings on the same patient, in the same posture, when possible.

Meals.—There is a moderate rise in systolic pressure and pulse-pressure after meals, and the pulse-rate is increased.

Breathing.—Breathing deep and forced raises blood-pressure during expiration, often as high as 10 mm., and lowers it during inspiration. Quiet breathing has no effect.

Sleep.—During sleep the maximum pressure is lowered 10 to 20 mm., due to relaxation and vasodilation. The fall is most marked in minimal pressure.

Exercise.—Causes a rise in maximum (systolic) pressure, and an increase in pulse-pressure, the rate being also increased. If muscular exercise is severe, there may be a rise in blood-pressure of from 5 to 10 cm., depending on the amount of force exerted. If exercise is excessive and fatigue ensues, blood-pressure falls and the pulse-rate is slowed.

A proportionate decrease in both systolic and diastolic blood-pressure during the training period was noted by W. S. Middleton (Med. Rec., Oct. 16, 1915). With a period of rest succeeding the training period there occurs a rise of systolic and diastolic blood-pressure beyond the anteseason records. The blood-pressure reaction to the given test of 50 stationary running steps is scarcely altered by a period of training. J. H. Barach and W. L. Marks (Arch. of Internal Med., Sept., 1914) found that in 88 per cent. of a series of 629 cases, the pulse pressure ranged between 20 and 70 mm. Hg. There was no constant relation between pulse and diastolic pressure, nor between physical efficiency (meaning also circulatory efficiency) and the ratio of pulse-pressure to diastolic pressure.

Report of observations made upon 500 applicants for aviation service. The readings were made with the men recumbent, standing, and after an average of 1600 foot pounds of work in 5 seconds. The average age was 24.2 years and the average readings in recumbency: pulse rate, 85.4; systolic pressure, 127.7; diastolic, 84.1; pulse-pressure, 42.2; and the lengths of the several phases averaged: first, 12; second, 24.5; third, 6.2, and fourth, 5.1 mm. Hg. After exercise the averages showed characteristic responses. The pulse rate averaged 112, systolic pressure, 145.4; diastolic, 90.6; pulse-pressure, 54.1; first phase, 13; second, 33.5; third, 11; fourth, 7 mm. Hg. and the average recovery time was 4.4 minutes. The area of cardiac dullness was never increased by the exercise, while 69 per cent. showed an apparent decrease. One hundred of the men showed some variation from the normal. Five had a cardiac murmur, and all of these showed an increase in cardiac dullness after exercise, labored breathing, and 3 some tonal arrhythmia. The tests gave some indication of myocardial weakness, but this was better shown by the change in the cardiac area after exercise, the dyspnea and the prolongation of recovery time to from

10 to 15 minutes. Similar findings were noted in 5 cases with palpable radial arteries. The conclusions reached were that the various blood-pressure findings alone were of relatively little importance in determining physical fitness, but that the added information given by some form of measured exercise was of definite value. The increase in pulse rate after exercise was not found of value. B. Smith (Jour. Amer. Med. Assoc., July 20, 1918).

Nervous and Mental Stimuli.—

Pain, anger, emotion, and mental effort stimulate vasoconstriction and cause a rise in blood-pressure, especially marked in minimal (diastolic) reading. The pulse is also quickened.

Blood-pressure is also affected by two pathological conditions, not in themselves diseases:—

The role of emotions is well shown by Dearborn (Med. Record, Sept., 16, 1916), who states that it is only by repeating the measurements each minute (or each 2 minutes) for a half-hour or less, and on several successive days, care being taken in interpretation to avoid all known sources of high pressure, that a correct estimate may be obtained. He found that it raised by tones of unpleasantness, and notably by anxiety; that in some cases, but by no means all, it appears to be lowered by all relaxing and pleasurable sensations; that it is, in general, variable in adults as in children, even during old age; that the deliberate relaxation of the voluntary muscles readily and greatly lowers the pressure.

In observations made during 8 months in 20 subjects aged 36 to 40 years, at the front, the writer found that explosion of a large shell close at hand caused a distinct rise in the systolic, diastolic, and pulse-pressure, which returned to normal within an hour. Fatigue and overwork always lessened the pulse-pressure, and nearly always increased the diastolic. Blood-pressure measurements are considered to afford the best criterion of fatigue requiring

rest from active duty. P. Ménard (Bull. de l'Acad. de méd., Oct. 17, 1916).

1. **Edema.**—Here the reading may be too high, due to the pressure required to squeeze the fluid out of the tissues. Hansen reports in one case an error of 20 mm. Hg.

2. **Asphyxia.**—Here also we obtain an extreme rise of pressure, and in slighter grades of deficient oxygenation of the blood, a rise to a less degree.

This condition must be considered in diseases of the lung, laryngeal diphtheria, etc.

The experimental studies showed that during vomiting, there is sometimes, according to Brooks and Luckhard (Amer. Jour. of Physiol., Jan., 1915), a period of elevated pressure, but more frequently a sudden and enormous drop in blood-pressure with cardiac inhibition at the moment of emesis, always periods of great oscillations in the blood-pressure. These great and sudden oscillations of the blood-pressure may cause a rupture of the blood-vessels which would occur with the same pressure but with slower changes.

Time Consumed in Taking Readings.—If constriction is continued over vessel for one minute, one may get a possible rise of 5 mm. Hg. Continued compression may cause a rise up to 20 mm.

Precautions.—Take all readings on the same patient at the same time of day, preferably midway between meals. Have the patient in a comfortable position, with muscles relaxed, best reclining, but in any case make all subsequent observations in the same position. Exclude all excitement, and see that patient is mentally composed and breathing quietly. Make the determinations as rapidly as possible. If the above precautions are observed, from a clinical

standpoint there will be no important error in the pressure values, providing the apparatus is accurate and the auscultation method properly employed.

The diurnal variations in arterial pressure should be taken into account when clinical readings are taken at intervals to obtain a correct estimate of the progress of a given case. Thus Weyssse and Lutz (*Amer. Jour. Physiol.*, May, 1915) in a study of the diurnal variations in arterial blood-pressure found that a rise of maximum pressure averaging 8 mm. Hg. occurs immediately on the ingestion of food. A gradual fall then takes place until the beginning of the next meal. There is also a slight general rise of the maximum pressure during the day. The average maximum blood-pressure for healthy young men in the neighborhood of 20 years of age is 120 mm. Hg. This pressure obtains commonly one hour after meals. The higher maximum pressures occur immediately after meals, and the lower, as a rule, immediately before meals. The range of maximum pressure varies considerably in different individuals, but the highest and lowest maximum pressures are practically equidistant from the average pressure of any one individual. The minimum blood-pressure is very uniform throughout the day, and is little affected by the ingestion and digestion of meals. When it is affected a rise or a fall may take place. There is a tendency for a slight general lowering of the minimum pressure throughout the day. The average diastolic blood-pressure for healthy young men in the neighborhood of 20 years of age is 85 mm. Hg. Thus the authors get an average pulse-pressure of 35 mm. Hg. Pulse-pressure, pulse-rate and the relative velocity of the blood flow are increased immediately on the ingestion of meals. They attain the maximum, as a rule, in half an hour, and then decline slowly until the next meal. There is a general increase in each throughout the day. The average pulse rate in the authors' investigations proved to be 72 beats per minute.

As to the significance of variations, in addition to that mentioned above, New-

man and Fischer (*Wash. Med. Annals*, Sept., 1914) believe that a fall in blood-pressure associated with decreased pulse-pressure is indicative of heart failure; whereas a fall in pressure associated with increased pulse-pressure is indicative of hemorrhage or shock. Slight changes in the systolic and diastolic relation are not to be relied on. Cases should be observed frequently in order that the state of the circulation be understood. The systolic and diastolic blood-pressure should be taken on all surgical cases, before, during and after the operation.

In a study of 43 tuberculous patients seen by F. C. Smith (*Jour. Amer. Med. Assoc.*, May 29, 1915) the effect of altitude on blood-pressure was not great. A tabulated statement of the result as regards hemoptysis of various degrees failed to support the contention that hemoptysis depended on high systolic pressure. It seems extremely doubtful whether moderate altitude has any pronounced effect on tuberculosis, except possibly in patients whose circulatory apparatus is unable to accommodate itself to the increased strain put on it. P. Schrumphf (*Deut. Arch. f. klin. Med.*, cxiii, 466, 1914) holds that many patients with circulatory troubles are actually benefited by a stay at an elevation of 2000 meters or less. The usual reason against altitude, that the blood-pressure will be raised as the atmospheric pressure becomes less, he regards as fallacious. Normal pressure is unaffected by an ascent to 2000 meters. In a group of 13 patients with slight arteriosclerosis and hypertension, but without serious renal disease, the writer has always found fall in pressure, the decrease amounting to 25 to 55 cm. water. Similar results were obtained in patients with marked arteriosclerosis.

A study of the viscosity of the blood and blood-pressure in 19 cases in which the pressure was abnormally high in all but 2, showed no special connection between the two conditions could be detected except that when the pressure was low the viscosity was generally low also. Bucco (*Riforma Medica*, Mar. 28, 1914).

Experiments on cats in which either heat or cold representing a

difference of 25° C. above or below the body temperature was applied either to the outside or to the interior of the abdomen while the blood-pressure of the animal was being constantly recorded. Each application lasted only 15 minutes. When applied externally cold produced little or no effect, while heat caused a material elevation in the blood-pressure, which was maintained throughout its application. When applied within the abdomen both heat and cold produced a marked fall in the blood-pressure. F. S. Hammett, E. W. Tice, and E. Larson (Jour. Amer. Med. Assoc., Feb. 24, 1917).

The effects of tobacco in cigarette and cigar smoking were found by the writers to correspond. There was an average increase in pulse rate of 13 beats per minute. Whereas the risk from any elevation in blood-pressure increases greatly the higher the initial pressure in the patient, it is undesirable for anyone having a constant systolic pressure much above 200 to smoke. Again, smoking is equally undesirable for anyone having a constant initial pressure above 160 mm. when the use of tobacco is found uniformly to produce a considerable rise in blood-pressure. Thompson and Sheldon (N. Y. State Jour. of Med., Feb., 1917).

BLOOD-PRESSURE IN DISEASE.—Blood-pressure in disease may be either high (hypertension) or low (hypotension), as the case may be:—

Hypertension.—First considering hypertension, we find that, where it is not due to the factors we have just considered, or secondary to drugs, as digitalis, adrenalin, strychnine, ergot, etc., there is an increased peripheral resistance in the blood-vessels, which has been found to depend largely on the splanchnics. Another important point is the fact that continued high pressure cannot

be maintained without cardiac hypertrophy, and that the increased tension will of itself cause changes in the vessel wall, thickening of intima and media, and loss of elasticity, with danger of rupture.

Referring to a study of 9000 cases by an insurance company, has shown that the 3 classes of affections especially marked by low blood-pressure were tuberculosis, nervous, and gastrointestinal diseases. In fact, in all the respiratory diseases the blood-pressure was found to be below the normal 126 mm. Hg., and in one instance the presence of an unusually low pressure had led to a careful examination of the patient, the result of which was that a tuberculosis was discovered which would not otherwise have been detected. L. F. MacKenzie (N. Y. Med. Jour., Sept. 26, 1914).

After a study of over 500 patients manifesting various degrees of vascular disease and cardiac disability, the writer found that the types for the most part may be grouped under the following heads:—

1. *The cerebral or cerebrorenal type of hypertension*, which comprised those patients with vascular disease in which there were evidences of damage to the arteries in general and to kidneys in particular. A cerebral death occurred in a large proportion of these patients and the unfavorable prognosis seemed to depend upon the height of the diastolic pressure. In the patients of this group the arteries were rigid as well as contracted.

2. *The cardiac type of hypertension*, which comprised those patients without evidences of vascular disease and its associated nephritis. Death usually occurred from myocardial exhaustion. The arteries were rigid, but not contracted, or the diastolic pressure would have been increased. The prognosis seemed to depend upon the ability of the heart to sustain the increased systolic pressure as a purely compensatory measure.

3. *The cardiac type without hypertension but with increased pressure-ratio.* This group comprised valvular and myocardial lesions which necessitated increased cardiac work. The prognosis seemed to depend upon the ability to sustain an increased pressure-ratio. Death when it occurred was due to myocardial exhaustion.

4. *The cardiac type without hypertension but with decreased pressure-ratio.* This group comprised those patients with cardiac dilatation or those in whom marked evidences of myocardial exhaustion had occurred. The prognosis seemed to depend upon the reaction of the heart to stimulative measures in the endeavor to increase the pressure-ratio.

5. In general, too much reliance should not be placed upon blood-pressure variations as a guide to the condition of the circulation in any particular case, for such variations are of value only when associated with all other data. Certain groups of patients may, however, be differentiated in the manner above outlined, such differentiation possessing definite diagnostic and prognostic value. W. J. Stone (Amer. Jour. Med. Sci., Feb., 1917).

In *infectious diseases* a high diastolic blood-pressure indicates a tendency to paralysis of the larger abdominal vessels with accumulation of the blood in them, and hence this must be accepted as a sign of the severity of the infection. A lower systolic pressure with a lower diastolic pressure is not a sign that the heart is weakening but only that the vascular tonus is growing less. On the other hand, when the diastolic pressure rises while the systolic falls, this is a sign that the heart is weakening. Schwartzmann (Wiener klin. Woch., July 23, 1914).

As regards hypertension, an analysis of 305 patients made by the writer showed that about 68 per cent. of those showing hypertension were in patients between 40 and 69 years of age, the greatest number occurring between the ages 50 and 59. Almost

three-fourths of the cases, 72.8 per cent., had definite signs of chronic nephritis. Arteriosclerosis was also common. The next most common conditions were circulatory disturbances, chronic myocarditis or valvular lesions. Albumin is usually to be found at some time in cases of hypertension. If it is persistently absent, the cause of the high blood-pressure is generally vascular or cardiac disease, and not renal. In hypertension cases with a normal heart load of 40 to 60 per cent., 85 per cent. had chronic nephritis. Of those cases in which the load was under 40 or over 60 per cent., only about 70 per cent. were cases of nephritis. When the load was under 40 per cent., the prognosis proved to be most unfavorable, but there were several cases without signs of cardiac decompensation. Among those whose heart load was 40 to 60 per cent., only 28 per cent. gave signs of cardiac decompensation; of those whose heart load was 61 to 99 per cent., there were 59 per cent. with cardiac decompensation, and of those whose load was 100 per cent. or more, 66 per cent. showed signs of cardiac decompensation. Hypertrophy of the heart without decompensation was most common in cases with a normal load; when the load was 100 per cent. or over, there were the fewest cases of heart hypertrophy without decompensation and the greater number of decompensated hearts. Subnormal diastolic pressures suggest the presence of aortic regurgitation and the absence of chronic nephritis.

In cardiac decompensation the effect of *digitalis* was rather to increase pulse pressure and systolic pressure and cause a fall in the diastolic pressure. Deaths in hypertension patients occurred most frequently between the ages of 40 and 60 years, and the underlying condition was either chronic nephritis or chronic disease of the heart, or a combination of the two. More than half the deaths occurred with symptoms of uremia or apoplexy. Twenty-

eight per cent. died with signs of progressive heart failure. The patients in more than half the fatal cases had had a systolic pressure of over 200 mm., and 86 per cent. had had diastolic pressure of over 100 mm. Cadbury (*Jour. Amer. Med. Assoc.*, from *Arch. of Internal Med.*, Sept., 1916).

DISEASES WITH HYPERTENSION.

—Arteriosclerosis.—Here our diagnosis of the existence of sclerosis rests on the palpation of hardened vessel walls, visible tortuosity, or we may reason it is present from the sclerosed vessels in the eyeground, the enlarged left ventricle, ringing aortic second sound, and high blood-pressure.

Numerous observations have shown that unless the splanchnic vessels are affected there is not likely to be an increased blood-pressure and hypertrophy of the heart, but whenever the splanchnics are sclerosed the blood-pressure is increased.

In this condition the systolic pressure is greatly increased (150-170 mm. to 250 mm.). The diastolic pressure increases (110-130 mm.), but not proportionately, increasing the pulse-pressure greatly (60 mm. or over).

From the pathological standpoint, as T. C. Janeway observes (*Boston Med. and Surg. Jour.*, Aug. 26, 1915), the work of Fisher, indicating a normal increase of blood-pressure with age, the tendency being to regard 135 mm. as the midlife pressure, and 145 mm. thereafter, has tended to cause us not to view hypertension with so serious a prognostic eye. In the young adult or adolescent, observations carried out by R. I. Lee (*Boston Med. and Surg. Jour.*, Oct. 7, 1915) on the 662 members of the freshman class of Harvard, showed that at the average age of 18 years, with average height 5 feet 8 inches, and average weight without clothes 143 pounds, the average systolic pressure was ap-

proximately 120 mm. Hg., and the average diastolic pressure 80 mm. In the absence of other abnormal findings moderate increase of systolic blood-pressure seemed to be of no significance. The diastolic blood-pressure is much less subject to variation and is of considerable value in offering a control on an abnormal systolic pressure. Albuminuria was present in 5 per cent. of this group, and in only 1 case was there additional evidence of a true nephritis. Albuminuria in young male adults may be permanent, orthostatic, or transitory, and is apparently of no serious significance.

When the diastolic blood-pressure is not raised above 90 mm. Hg., there exists no vascular degeneration, however high the systolic reading. There are, however, 3 classes of exceptions to this: (1) marked aortic regurgitation; (2) severe mitral regurgitation with considerable cardiac hypertrophy; (3) an indefinite group found in people past middle age or of advanced years, who, notwithstanding the fact that their vessels are markedly thickened and systolic pressure is high, exhibit a normal or nearly normal diastolic pressure. Thorne (*Pract.*, Nov., 1918).

“Angiosclerosis” a term applied to a rather common class of patients who have a permanent high blood-pressure with no signs of sclerosis or nephritis, even after repeated examinations. Janeway associated it with an early chronic interstitial nephritis.

Its early discovery is very important in order to prevent cardiac hypertrophy and vascular changes, which are inevitable if the condition of high tension is not relieved.

Treatment.—Here it is important to regulate the diet, eliminate as far as possible overwork and worry, keep the intestinal tract open, and the bowel function active, as many of these cases are due to a certain amount of autointoxication. Sweating is also of value.

Vasodilators should not be used until all other methods fail, or the pressure is such that it demands immediate relief, there being danger of rupture of the vessels; then use nitrites, and if necessary bleed. High blood-pressure is often compensatory and by lowering it harm is done.

In accord with many modern writers, the writer regards high blood-pressure pathological, but usually, if not always, physiological in meaning. It tends more to prolong life than to shorten it. If causes cannot be removed, it is not to be treated, being compensative. Brooks (N. Y. Med. Jour., July 25, 1914).

High blood-pressure may be normal for existing morbid conditions and should then not be interfered with, especially by drugs. Bishop's "**few protein**" diet and Kellogg's **vegetable protein diet** are of value, as are also the clearing of the intestinal tract and the production of elimination by **salines** and **alkalies** and **mineral water baths**, while tea, coffee, alcohol and tobacco are best omitted. The **Saratoga waters**, Moriarta believes, exert their greatest benefit from their radium content, their use almost invariably causing a drop of 20 to 60 mm. Hg. in 4 to 6 weeks. **Radium** causes stimulation of normal cells as well as correction of perverted cell action by influence on the enzymes. The writer has treated 56 cases in the past year with radium emanation combined with **radioactive waters** and regulated régime. The radioactive waters are given in doses of 25,000 to 100,000 Mache units a day, in divided doses after meals and at bedtime, while inhalations are given for 2 hours daily in an emanatorium, which shows 250 Mache units to the liter of air. In selected cases radium salts are given intravenously and repeated in 2 weeks. D. C. Moriarta (Med. Rec., May 13, 1916).

In all cases of abnormal arterial blood-pressure we should remember that hypertension has, on the whole,

a far more unfavorable prognosis than hypotension, which, except after loss of blood, in shock, in acute cardiac dilatation in the course of infective diseases, is not a cause of immediate alarm. For the most part, hypotension indicates mathematically the degree of exhaustion in wasting diseases, such as tuberculosis. On the other hand, hypertension is usually associated with arteriosclerosis, when the degree of it measures the danger from nephritis or cerebral hemorrhage. Satterthwaite (Internat. Clinics, vol. iii, Series 27, 1917).

The effective treatment of hypertension is prophylaxis. **Mental** and **physical rest** seems the main factor. A **diet**, regulating quantity rather than quality, is also indicated. Mosenenthal (Jour. Amer. Med. Assoc., Nov. 23, 1918).

In patients with hypertension and presumably chronic interstitial nephritis, large amounts of fluids may cause a very decided increase in blood pressure, according to the promptness with which the kidneys excrete water. In 3 cases studied, large amounts of fluid daily for 6 days did not affect the urea nitrogen in the blood. In 2 of these, blood uric acid was definitely lessened, perhaps due to the treatment. Miller and Williams (Amer. Jour. Med. Sci., Mar., 1921).

Nephritis.—Chronic interstitial nephritis gives a high systolic pressure (200 mm. or higher), and a relative low diastolic pressure, giving a large pulse-pressure (60 to 80 mm. Hg).

Here hypertension is one of the most important signs, often making the diagnosis in obese individuals, where the enlargement of the heart is hard to define and the urine negative for a long time.

Dr. T. C. Janeway says: "Given a systolic pressure of over 200 mm., the diagnosis of contracted kidney must be disproved by repeated examinations before it is abandoned."

Caution.—If the heart has failed to compensate, the pressure may be low, and it is here that the pulse-pressure will aid materially. In this condition the pulse-pressure is lessened.

The prognosis depends not so much on the actual height of the mercurial column, but as to whether the pressure is rising or resistant to treatment. The ultimate danger is rupture and apoplexy.

Various data tend to show that there is no direct connection between the blood-pressure and morbid conditions in the kidneys, although abnormal conditions in both are almost invariably found parallel. There is much to sustain the assumption that an abnormally high blood-pressure is the primary disturbance, arteriosclerosis and vascular kidney affections occurring only secondarily. Hypertension is not, however, easily influenced. Moderate hypertension may subside under bed-rest and diet, but a high blood-pressure, 200 to 250 mm., never goes down permanently to normal; 170 mm. seems to be the extreme limit with which this is possible. V. Bie (*Ugeskrift for Laeger*, Mar. 4, 1915).

Chronic Parenchymatous Nephritis.

—In it the blood-pressure is uncertain, often being normal. When there is hypertension it often aids, but its absence does not negate the diagnosis.

Acute Nephritis.—The pressure varies greatly, in typhoid fever and pneumonia there being no increase in tension. In scarlet fever; however, there is a sharp, sudden rise, often of 50 mm., and it is a valuable aid to the diagnosis.

Uremia.—Here blood-pressure runs parallel with the symptoms, maximum pressure being very high, in some cases 290 mm. Hg.

Pressure falls with the alleviation

of the symptoms as a general rule, though it may fall before fatal termination, due to failure of the heart.

Apoplexy; Cerebral Thrombosis; Depressed Fracture of the Skull; Fracture of the Base; Intracranial Hemorrhage; Tumors (Rapid-growing, Cerebral); Jacksonian Epilepsy (Cases of Increased Intracranial Pressure).—In these conditions of increased intracerebral pressure the highest blood-pressure readings occur; Hirschfelder gives systolic 300 to 400 mm.; diastolic 160 mm. or over; pulse slowed.

The high pressure is compensatory, and is the effort to supply more blood against increasing intracerebral tension, and thus prevent anemia of the brain.

The important point is not to bleed, and try to lower the pressure, but to operate where possible, and where not give atropine to paralyze the vagus, and allow the pressure to rise more rapidly.

In a case of head injury the blood-pressure reading is of great value; for in concussion the pressure is low, where in the above-named conditions it is invariably high, unless very late when cerebral paralysis has developed.

Angina Pectoris.—There are a large number of patients complaining of mild anginoid symptoms, tightness under the sternum, dyspnea on exertion, and belching after meals, which are accompanied by high blood-pressure. These are cases of mild angina pectoris. Given anginoid symptoms with marked hypertension (systolic 180 mm. or over) you are probably dealing with angina pectoris.

Aortic Regurgitation.—Here is found a systolic pressure 75 to 100

per cent. higher than the diastolic, the pulse-pressure being very high.

The pressure in some equals systolic 170 to 220 mm. Hg, diastolic 60 to 140 mm.; in other cases often systolic 120 to 130 mm., diastolic 50 to 60 mm.; but in all cases the pulse-pressure is great.

When you auscult over the artery in taking the blood-pressure reading you note a continuance of sound, so that the diastolic pressure in this case has to be determined by palpation.

Dr. Leonard Hill showed that in health blood-pressure is about the same in the brachial and femoral arteries, but in aortic regurgitation the readings from the femoral are much higher.

When the relation of pulse-pressure to the diastolic reading is low, in a doubtful case, it is not likely that there is aortic insufficiency.

Chronic Cardiac Hypertrophy.—Here we have an increase in both systolic and diastolic pressures (systolic 140-160 mm. Hg; diastolic 90 to 110 mm. Hg).

Cardiac Valve Lesions Other than Aortic.—Blood-pressure in these cases is about normal when compensation is good.

Heart with Loss of Compensation and Asthma.—Here is found high tension from associated asphyxia, when severe actual edema of lungs takes place and life is in danger; the blood being loaded with carbon dioxide immediate relief must be given, *e.g.*, bleeding, amyl nitrite, nitroglycerin, and later, after acute condition is relieved, give cardiac stimulants.

Myocarditis.—On exertion there is often an initial rise of blood-pressure, not well maintained, falling during

continued moderate exertion. In severe cases of myocarditis pressure often falls from the beginning. This is a very good means of determining the condition of the heart muscle. Take the pressure reading, then give mild exercise, taking several blood-pressure readings and compare with the level observed before exercise was begun.

In addition there are myocarditis cases of large, weak hearts with dyspnea, edema, and subjective symptoms: 1, with hypertension; 2, without hypertension. 1. These are cases secondary to Bright's disease or arteriosclerosis, or are primary myocarditis cases which have developed Bright's. 2. These are primary uncomplicated cases of myocarditis or the terminal stage of the secondary type. The primary cases usually show a high normal blood-pressure, and are more liable to have edema (systolic 135 to 145 mm. Hg).

Acute Endocarditis.—It is associated with a low systolic pressure.

Bradycardia.—Here the pulse-pressure is increased.

Idiopathic Epilepsy.—It is associated with a slow pulse and a high blood-pressure, which falls with the termination of the attack, and is an aid in the differential diagnosis of the postepileptic state and uremia, where there would be a maintained pressure during coma.

Gout gives increased tension both during the attack and also between attacks, when arterial changes are marked.

Plumbism.—Both acute and chronic cases show a well-marked high tension. In doubtful cases, where there is high tension, examine for signs of plumbism.

Exophthalmic Goiter.—Blood-pressure is variable, but as the disease is often accompanied by a hypertrophied heart the systolic pressure is often raised, *e.g.*, systolic 140 to 160 mm. Hg; diastolic 90 to 110 mm. Hg; pulse-pressure 30 to 50 mm. Hg; pulse-rate 120 or more.

Eye Disease.—In primary glaucoma tension is markedly increased, but not in secondary glaucoma, making a good differential diagnosis. Arterial hypertension is often a cause of early retinal and arterial changes in the eye.

It is often of the greatest value to determine high blood-pressure in eye work, for in cataract enucleation with high blood-pressure postoperative interocular hemorrhage and blindness can be prevented by a preliminary bleeding which will reduce the tension for a few days, allowing the eye to accustom itself to its new condition. Also by proper treatment advancing ocular changes may be prevented when associated with high tension.

Obstetrics.—Most authorities agree that at the end of pregnancy there is normally a rise in systolic blood-pressure (10 to 15 mm. Hg), with little change in the diastolic; although Starling, who reported the results of cases over a five-year period, believes the blood-pressure remains normal.

A fact recognized by all authorities is that the toxemia of pregnancy in the later months is accompanied by a rising blood-pressure, and that it is often present some time before any other signs or symptoms.

In pregnancy the following figures have been given for normal cases: Starling, systolic pressure, 110 to 120 mm. Hg. J. C. Hirst, systolic pres-

sure up to 7½ months, 118 mm. Hg; middle of last month, 124 mm. Hg.

The whole subject is well summarized in a paper by the above writer, in which he says:—

"1. Normal blood-pressure in the non-pregnant is 112 mm.

"2. Normal blood-pressure in the healthy pregnant is 118 mm.; in the last month slightly higher.

"3. Blood-pressure in toxemia in the first half of pregnancy associated with pernicious vomiting is invariably low.

"4. Blood-pressure in the toxemias in the latter half of pregnancy associated with albuminuria and eclampsia invariably high.

"5. High and rising blood-pressure is an invariable and early, often the earliest, sign of toxemia in the latter half of pregnancy.

"6. Upon rupture of the membranes there is an immediate fall of pressure,—60 to 90 mm. This fall is temporary only, but is attended with marked relief in headache and epigastric pain these patients so often complain of. Relief lasts for some hours, during which there is a gradual return to the previous level.

"7. There is a second fall (60 to 90 mm.) after the child is born. This again is temporary and is 15 to 30 mm.; if the patient has not bled profusely, the pressure is back to somewhere near the previous level before birth.

"8. Usually blood-pressure is high for forty-eight hours after birth, then begins to subside and reaches normal (118 to 124 mm.) in seven to ten days.

"9. A blood-pressure below 125 mm. should be disregarded; 125 to 150 mm. needs careful watching and moderate eliminative treatment. Over

150 mm. needs active eliminative treatment and probably will, especially if there is a tendency to climb higher, require induction of premature labor."

Starling in treatment advocates, before using more drastic methods, rest in bed on a carbohydrate and milk diet, with 1 teaspoonful of bicarbonate of soda four times a day, with 4 pints of liquid and thyroid extract in sthenic cases.

The blood-pressure remains high, after delivery and the relief of toxic symptoms, where there has been a previous nephritis. Hypotension also is important after delivery, in relation to the question of hemorrhage and shock, being markedly lowered in both conditions. This is especially important in relation to treatment. The question of whether the pressure is stationary, progressively rising or falling, and its relation to treatment are of more importance than absolute figures, though the latter serve as a good guide.

In a study of the systolic blood-pressure in pregnancy, based on 5000 consecutive cases, the writer found that the lowest systolic pressure recorded was 80, the highest 225 mm. Hg. In four-fifths of the patients it never fell below 100 or rose above 130, which, therefore, may be regarded as the normal limits for such cases. Any pressure above the normal high limit was found to be a sign of toxemia. F. C. Irving (*Jour. Amer. Med. Assoc.*, Mar. 25, 1916).

Therapeutics of Hypertension.—

The first and most important thing to regulate is diet, both as to amount and character of the food, avoiding animal proteids; to see that elimination is good; to be careful to look into and regulate the amount of

mental and physical strain used; in a word, to attend to general hygiene; to stop smoking and alcoholics. If this treatment is not sufficient, use potassium iodide in small doses.

Do not be in a hurry to lower tension in all cases, as it is often compensatory.

Mackenzie states that the nitrites are of little avail, as their action is too transitory. In cases of high tension with discomfort, as pain, and tightness across the chest, he uses potassium iodide in 5-grain doses four times a day, and finds that it often relieves the symptoms, but quite often does not lower the tension, though marked benefit is shown.

He also advocates chloral hydrate given in 5-grain doses two to three times a day, as well as in larger doses to produce sleep. This is especially beneficial in cases of angina pectoris.

Benzyl benzoate is a powerful vasodilator and does not depress the heart when given orally in small doses.* It is effective in hypertension and angina pectoris in 20 per cent. alcoholic solution, either in cold water or milk, 3 or 4 times a day. The reduced pressure is then maintained by giving very small doses, 5 minims (0.3 c.c.) of the 20 per cent. solution. D. I. Macht (*N. Y. Med. Jour.*, Aug. 28, 1920).

In addition, in hypertension, eat slowly, with a twenty-minute rest after meals; use blue mass or calomel occasionally; use digitalis if the high tension is due to failing compensation, as it will restore the heart tone; in severe cases use absolute rest with massage. Rest, mental and physical, as in heart disease, is the most valuable means of treatment. In toxic cases treat with active purgation, hot-air baths, etc.

R. D. Rudolf recommends, when these means have failed and there are symptoms of cerebral trouble, to use bleeding or vasodilation; amyl nitrite; nitroglycerin, doses of $\frac{1}{100}$ gr. (action lasts one hour, tolerance soon formed); sodium nitrite (freshly prepared), doses of 2 gr. (action lasts two hours, no tolerance acquired); erythrol tetranitrate, doses of $\frac{1}{2}$ gr. (action lasts six hours, no tolerance acquired).

In addition we may use thyroid extract, 2 to 3 grs. *t. i. d.*; high-frequency electricity, unreliable and effect often transitory; baths, not much permanent effect, though a series may give a fair result, as they reduce toxemia by causing better elimination.

Extensive experience has led F. de Havilland Hall (Clin. Jour., May 20, 1914) to treat high blood-pressure cases as follows:—

For patients with a pressure of 200 mm. Hg. and upward who have been overworked mentally and physically, treatment should be commenced with a period of **absolute rest**. If there be a pulse of over 100 per minute, or signs of heart failure, rest is imperative, and the recumbent position should be maintained until the pulse-frequency has fallen to normal, and the signs of cardiac weakness have disappeared. But many of the cases of high pressure occur in people who take too little exercise. **Walking** is one of the best forms of exercise to be ordered. **Cycling** may be allowed if taken quietly. **Golf** may be allowed to nearly all patients, except those with advanced arteriosclerosis. The **methods of Schott and Oertel**, if used, should be carried out under the direction of physicians who have had special experience in this line. **Massage** the author has found extremely useful in patients unable to take sufficient exercise, but directions should be given that deep abdominal massage is most not desirable, the **massage** being almost entirely confined to the **chest and extremities**.

Warm baths, followed by vigorous fric-

tion of the skin, are very beneficial. If the patient has been accustomed to Turkish baths, he may continue their use with advantage, but one should hesitate to allow a patient with high pressure to take his first Turkish bath.

In case of *insomnia* the **wet pack** at 70° F. often has a very soothing effect. It answered better than anything else in a patient the author saw, who had a pressure of 250 mm.

The **electric light bath** is very useful in many cases, stimulating the cutaneous vessels and causing sweating; the patients usually experience a sense of well-being afterward.

From the **Nauheim treatment** the author has seen the greatest benefit in suitable cases, but it is a two-edged sword, and is contraindicated in advanced arteriosclerosis, chronic nephritis, and intrathoracic aneurism. It should be carried out only under the observation of a physician with special experience.

A period of starvation benefits some patients, while in some cases it is difficult to induce the patients to take sufficient nourishment. Speaking generally, the most suitable **diet** for arteriosclerotics with high pressure is one mainly composed of **vegetables, farinaceous articles and milk**, while substances rich in nitrogen, and especially butcher's meat, should be avoided. In some dyspeptic patients the author has advised $\frac{1}{2}$ pint (250 c.c.) of **soured milk** to be taken 3 times daily, with great benefit. He limits the amount of salt taken as much as possible, and prohibits salted meat and fish.

The author favors distributing the daily amount of food over 4 meals of about equal value, viz., breakfast, luncheon, tea, and dinner. The 2 best meals in the day should be breakfast and luncheon; tea should consist of some bread and butter or plain biscuits with weak tea, or better, cocoa, or milk and water; dinner should be a light meal—a little fish and vegetable with a milk pudding, for instance.

The condition of the gums and teeth needs careful attention, pyorrhea alveolaris being one of the causes of high tension.

Calomel and blue pill are useful not only as aperients, but also have a remark-

able effect in lowering blood-pressure. A teaspoonful of **Epsom** or **Glauber's salts** may be taken in half a tumblerful of warm water before breakfast, or one of the mineral waters. A tablespoonful of pure **paraffin** taken at night acts pleasantly and efficiently.

Next to the aperients come the **iodides**. Some patients tolerate the **sodium salt** better than that of potassium. If neither seems to suit, **iodoglidine** may be tried. The author orders small doses—3 grains (0.2 Gm.) to be taken 3 times daily for months or even years.

In patients with a *syphilitic* history the Wassermann reaction should be tried, and, if positive, **mercury** administered, preferably by inunction, followed by **potassium iodide** in full doses.

High blood-pressure is often met with at the *menopause*, and is frequently accompanied by obesity; in such cases small doses of **thyroid gland**, together with a combination of **bromide** and **iodide of potassium**, are most useful in diminishing weight, lowering tension, and relieving the patient of the flushes and fulness in the head.

If the iodides are badly borne **potassium** or **sodium nitrite** in 1- to 2-grain (0.06 to 0.12 Gm.) doses may be tried, though doses up to 5 grains (0.3 Gm.) have been warmly advocated. In solution they are unstable, so are best ordered in chocolate tablets. In a few cases Hall has obtained much benefit from the administration of the **hippurates of ammonium** and **lithium**. Of the latter, 3 or 4 grains (0.2 to 0.25 Gm.) may be given daily. The ammonium salt is less powerful, and 6 to 7 grains (0.4 to 0.45 Gm.) may be given daily. In *rheumatic subjects* **sodium salicylate** should be ordered.

The more powerful and quickly acting vasodilators, such as **amyl nitrite**, **nitroglycerine**, and **erythrol tetranitrate**, the author reserves chiefly for *anginal* or *dyspneal attacks* coming on in patients with high blood-pressure. In the very acute attacks inhalation of 3 minims of **nitrite of amyl** will often give immediate relief, and its action may be continued by giving $\frac{1}{100}$ grain (0.006 Gm.) of **nitroglycerine**. This dose may be increased up to $\frac{1}{40}$ grain (0.006 Gm.). A patient took 10

minims (0.6 c.c.) of the official 1 per cent. solution 3 times a day for some weeks. Eventually it failed to give relief. The author has found **erythrol tetranitrate** in doses of $\frac{1}{4}$ grain (0.016 Gm.) most useful in patients who get anginal symptoms on starting to walk. The drug should be given a quarter of an hour previously.

Blood-letting proved of the greatest service in certain cases of high blood-pressure. **Venesection** is indicated where the patient is unconscious and cerebral hemorrhage is feared; likewise in convulsive cases attended with high tension.

The author emphasizes the value of the sphygmomanometer in cases of *coma* as an indication in the employment of **venesection**; by this means one may be able to distinguish between coma due to hemorrhage and that caused by thrombosis, the blood-pressure being invariably low in the latter condition.

HYPOTENSION.—Here we find, as a rule, not so much cardiac weakness as failure of the vasomotor center.

As regards the meaning of this condition, Cornwall (N. Y. Med. Jour., Mar. 7, 1914) reports 13 cases of low blood-pressure from which he draws the following conclusions: 1. A low systolic pressure, with correspondingly low diastolic pressure, does not necessarily mean poor circulation; it does imply a diminished reserve power of the circulation. 2. A low systolic pressure, with comparatively high diastolic pressure, and therefore a small pulse-pressure, usually means myocardial weakness with chronic nephritis, arteriosclerosis, or arterial spasm, and may be prognostically bad. 3. A low diastolic pressure, with comparatively high systolic pressure, and therefore an excessively large pulse-pressure, may mean several things: A purely functional condition, a compensated aortic regurgitation, myocardial degeneration without arteriosclerosis or nephritis, toxic irritability of the myocardium, or vasomotor dilatation from any cause. 4. The diastolic pressure seems to be more stable than the systolic, and to show less often marked variations from its normal, without definite pathological cause; the systolic pressure seems to accommodate itself to the diastolic

more easily than the reverse. The diastolic pressure indicates the peripheral resistance, which in many cases is determined by permanent pathologic conditions. Increase of diastolic pressure beyond normal limits causes pulse-pressure to assume an overload if adequate circulation is kept up. 5. Vasodilator drugs may improve the circulation by increasing the pulse-pressure. 6. Cardiac depressant drugs may lower the diastolic pressure by diminishing the systolic force and calling for a pulse-pressure overload. 7. Acute and chronic toxemias can produce low blood-pressure by dilating the blood-vessels and by weakening the myocardium, but their effect is more often produced by vascular dilatation, either through the vasomotor center or locally. 8. Chronic tobacco poisoning is a very common cause of persistent low blood-pressure.

In the treatment of *hypotension*, the writer lays stress on **removal of cause**, if possible, and the importance of **rest** for patients with chronic myocardial degeneration, especially if there is circulatory insufficiency on slight exertion, when they must be kept very quiet, though many may be allowed to walk around, **avoiding stairs and speed**; persistent low pressure following typhoid or any acute infection demands prolonged **rest in bed**. If the circulation is weak, heart stimulants (**strychnine, strophanthus, and caffeine**) are indicated. Low diastolic pressure with fairly healthy myocardium requires **digitalis**, but it is contraindicated when myocardial degeneration and relatively high diastolic pressure are present. A severe, sudden fall of diastolic pressure due to toxic vasomotor dilatation, should be relieved by **adrenalin** and **pituitrin**. If due to hemorrhage, the prompt use of **normal saline infusions** and **elevation of extremities** is needed. Conwell (N. Y. Med. Jour., Mar. 7, 1914).

Acute Infectious Diseases.—These all have low tension except meningitis. The fall of pressure is mainly due to vasomotor depression or paralysis from the toxins, and, to a

less extent, from a damaged heart muscle, due to the same cause.

Typhoid Fever.—Here we have one of the lowest pressures occurring in disease: Often systolic 100 to 120 mm. Hg; diastolic 60 to 90 mm. Hg. The systolic has been as low as 75 mm. Hg.

The fall in pressure is gradual, and takes place progressively (Janeway), *e.g.*:—

First week, systolic	115 mm. Hg.			
Second " "	106 " "			
Third " "	102 " "			
Fourth " "	98 " "			
Fifth " "	96 " "			

Here the value of routine blood-pressure observations is very great, both to determine the effect and amount of treatment required, and also to be able to note the onset of complications.

In hemorrhage there is a sharp, sudden fall, due to a lessened volume of blood. In perforation just the opposite takes place, the irritation of the peritoneum causing a reflex vasoconstriction and a sudden, sharp rise in blood-pressure.

The work of Briggs and Cook showed in 1 case a rise of blood-pressure hours before there were any other definite signs of perforation. The diagnosis was confirmed by operation. But, as they demonstrated, you do not always obtain a rise in blood-pressure, for the vasomotor center may be exhausted, in which case there will be no rise. Therefore a lack of rise in blood-pressure does not negate other signs and symptoms of perforation, but when present it is reliable, unless pneumonia develops.

Using blood-pressure in conjunction with treatment they found baths, when favorable, produced a rise in

blood-pressure. Of the drugs strychnine and digitalis were the best to combat collapse. When used for a quick result, strychnine gr. $\frac{1}{10}$ to $\frac{1}{20}$ hypodermically was given, and the resulting rise in blood-pressure was maintained for an hour or so. When the pressure begins to fall, it may be maintained by a smaller dose.

Digitalin hypodermically was more certain than strychnine, with an initial dose of gr. $\frac{1}{10}$; its action taking place earlier, though not so long continued. It often gave a rise when strychnine failed. Permanency of results may be obtained by combining the two.

Alcohol was of no value as a stimulant, but lowered pressure; was of benefit solely as an alterative.

Thayer found, as a sequence of typhoid fever, a rather marked hypertension some years after the attack.

Pneumonia.—Here there may not be much change in the blood-pressure, though as the disease progresses there is a tendency for it to lower.

Hirschfelder: Systolic, 110 to 130 mm. Hg; diastolic, 90 mm. Hg; pulse-rate, 120.

Gibson, of Edinburgh, made a general rule which seems to work out well in patients who are not alcoholics, but does not apply to this class of patients. The rule is as follows: When the systolic pressure expressed in mm. of Hg is higher than the pulse-rate expressed in beats per minute, the condition of the patient is good. When the systolic pressure expressed in mm. Hg is lower than the pulse-rate per minute, the condition is serious.

Dr. Alexander Lambert in a recent article called attention to the fact that the blood-pressure varies greatly

in pneumonia, but that it is of the greatest value in determining whether the condition present is one of vasomotor paralysis due to toxins, in which case the blood-pressure will be found to be low; or whether the patient is suffering from high tension with cardiac failure imminent.

About one-half the cases die of vasomotor paralysis, the other half from failure of the heart. In the one, adrenalin, camphor, strychnine, and digitalis are indicated; in the other, relief of the high tension with vasodilators or bleeding is indicated.

The matter is very tersely expressed by Dr. H. A. Hare when he says: "If the vessels be at fault the difference between diastolic and systolic pressure will be marked, the heart if strong sending out a forcible wave of blood in an endeavor to fill the blood-paths. On the other hand, if the pressure be low from a failing heart, there will be little difference between diastolic and systolic pressure, for obvious reasons."

Diphtheria; Acute Rheumatism; Scarlet Fever; Measles.—These all show a slightly lowered blood-pressure. The systolic pressure usually falls below 100 mm. Hg (Weigert).

In scarlet fever, if acute nephritis develops, there will be a sharp rise,—a good diagnostic point.

Phthisis.—Here we usually find a low systolic pressure; systolic 90 to 100 mm., though it may vary between 80 and 120 mm.

Blood-pressure from the standpoint of prognosis and treatment is of considerable value; though as to diagnosis there is a marked difference of opinion, many thinking it of doubtful value before physical signs have developed.

Given a patient with tuberculosis, a falling blood-pressure is a bad sign, while a rising blood-pressure toward the normal is equally favorable.

When the blood-pressure has reached the normal and remained there, we may feel pretty confident our case is well; so that in supposedly cured cases it is important to take the blood-pressure observations to determine whether there is any recurrence of the disease.

Given a patient with a persistent low blood-pressure, always consider the probability of tuberculosis very seriously, especially where other causes for the low tension cannot be determined.

Lauder Brunton regards low tension as due usually to, 1, beginning phthisis; 2, excessive smoking; further stating that where smoking can be excluded always examine the lungs carefully for tuberculosis.

Dr. Haven Emerson warns us that persistent low tension should put us on guard to prevent tuberculosis, especially where the patient is under unhygienic conditions.

Diarrhea; Dysentery; Cholera; after Profuse Vomiting, as in Carcinoma of the Stomach, Intestinal Obstruction, Peritonitis, etc.—Here we find marked low blood-pressure, as the arteries are depleted of fluid. Here blood-pressure determinations are valuable in following treatment and as a means of determining impending shock or collapse.

Cancer; Chronic Phthisis; Anemias, etc.—There being associated brown atrophy of the heart as a consequence, there is low blood-pressure in all of these conditions, the systolic being 10 to 20 mm. lower than normal.

Pericarditis and Acute Cardiac Conditions.—Here pressure is low, the vasomotor center being depressed by the toxins of the disease, and there is also some weakness of the heart muscle. The systolic pressure varies from 98 to 140 mm.

Acute Infections of Children.—Here Briggs and Cook found blood-pressure determinations of the greatest value in prognosis and treatment. If pressure is falling there is danger of collapse and it is an indication for active stimulation.

They concluded that systolic pressures of 60 mm. during the first year and 80 mm. in older children were the danger lines calling for active stimulation.

Treatment.—In collapse with cyanosis they used a mustard bath, and found that strychnine and digitalis were the most reliable drugs.

Prognosis.—A short-lived response to treatment with a renewed fall is a bad sign.

Syphilis.—There is a hypotension during the acute stages due to the toxemia of the disease.

Tabes Dorsalis.—Pal concluded that with the lightning pains there was a marked fall in blood-pressure; in contradistinction to gastric crises, where there was an enormous rise. He assumed that as there was marked hypertension the splanchnics must be involved, and advised the use of chloral to relieve the condition, on account of its blood-pressure lowering qualities.

The association of high tension with gastric crises aids in a differential diagnosis, as there are only two other conditions of pain in the abdomen with high tension: 1, lead colic; 2 angina abdominalis of arteriosclerosis.

Neurological Conditions.—(a) *Melancholia* elevates blood-pressure in proportion to the symptoms, and is relieved by vasodilators, improvement occurring coincidentally with the lowering of pressure.

(b) *General Paresis*.—Here in the early stage blood-pressure is normal, while in the late it is low.

(c) *Acute Mania*.—Here blood-pressure is low and after an attack lower still, due to exhaustion.

(d) *Trifacial Neuralgia* is accompanied by a high blood-pressure.

(e) *Insomnia* may be associated with either one of two conditions: 1, high tension (systolic 130 to 150 mm. Hg); 2, without high tension. In the first vasodilators act as hypnotics and are indicated; sleep takes place as the pressure falls. In the second class sulphonal, trional, and similar drugs are more effective.

(f) *Neurasthenia, Hysteria, etc.*—Pressure here is variable, but becomes high readily, owing to the nervous stimulation of the vasomotor center.

(g) *Alcoholic Delirium*.—Here pressure is lowered 30 to 40 per cent.; therefore we must use care in the employment of hot packs to quiet these patients, as we may cause collapse.

Shock and Collapse.—Here we have a very marked and dangerous fall in blood-pressure, due to vasodilation, from peripheral nerve stimuli to the vasomotor center. Henderson claims the vasomotor depression is due to overaëration and lack of carbon dioxide to stimulate the center. Here at times the systolic pressure has been as low as 40 to 60 mm. Hg.

Cook and Briggs proved that the

vasomotor center was not exhausted, for by the use of strychnine and digitalis they were often able to save apparently hopeless cases; that adrenalin intravenously will raise the pressure, but that its action is fugacious; that an intravenous saline injection is of no value to raise pressure unless adrenalin is added, and that $\frac{1}{4}$ to $\frac{1}{2}$ gr. of cocaine hypodermically will give an almost immediate rise of blood-pressure (10 to 20 mm.) and maintained from one to three hours.

Extensive Hemorrhage.—In this case there is a marked fall due to the loss of volume of blood. This condition is treated by intravenous saline injection, after the bleeding point is secured.

Surgery and Anesthesia (Briggs and Cook).—(a) *Ether* increases the blood-pressure in the first stage, reflexly from the irritation of the mucous membrane. During the second stage the pressure also rises, owing to the muscular activity. In deep anesthesia the pressure level falls to just above the normal.

(b) *Nitrous Oxide*.—Here there is a rise of pressure due partly to asphyxia. When used with ether there is an initial rise, but the second increase of pressure is eliminated, because the stage of muscular activity is avoided.

(c) *Chloroform*.—Blood-pressure falls from the start, and remains low, except in pregnancy.

If during anesthesia shock or collapse is imminent, there is a marked fall in blood-pressure before other signs are manifest; hence the value of taking blood-pressure readings every five minutes during the administration of an anesthetic. If pressure

falls, correct any faulty administration of anesthetic; if the pressure then rises, proceed.

If the pressure continues to fall, or remains at a dangerous level, use active measures, and terminate operative procedure as rapidly as possible. There is less shock by continuing the ether than to allow patient to come out and renew the anesthetic. With a dangerous fall in blood-pressure while using chloroform, withdraw the anesthetic at once.

Spinal Anesthesia (Cocaine).—You may have a dangerous fall due to paralysis of the upper dorsal region.

Operative Procedure.—Cutting or manipulative procedures cause a transitory rise in blood-pressure of about 10 mm., due to the pain impulses conveyed to the vasomotor center; it may rise again, remain low, or fall farther to shock. If cocaine is injected into the nerve-trunks during anesthesia there is less danger of shock.

By blood-pressure determinations we have the most accurate means, not only of determining shock, but also its extent and reaction to treatment. The blood-pressure readings should be taken routinely, not only during the operation, but also before and after. Before operation often a case has a high tension, which might become dangerous if an anesthetic were administered, unless it were lowered by preparatory treatment. After operation routine observations are of value in determining the onset of shock or hemorrhage.

In addition, in pleural and peritoneal effusions, there is a rise of blood-pressure. Aspiration produces a fall, which can be determined by blood-pressure examinations and the

aspiration stopped if the fall becomes dangerous.

Individual blood-pressures show slight increase due to excitement, and from 10 to 30 mm. increase during induction of etherization, after which the pressure falls to near the individual's level. This level, once reached, is maintained rather closely throughout anesthesia, barring changes due to oncoming shock, asphyxia, sudden cerebral anemia, or changes in the patient's position on the table. Struggling, depth of anesthesia and manipulation of organs, also influence the pressure to a less degree. In shock the pressure falls, usually gradually, while the pulse-rate rises. In asphyxia, at the outset the breathing is deepened, and there is a marked rise in blood-pressure. In cerebral anemia the pressure phenomena are exactly reversed and the fall is abrupt, very alarming, and accompanied by marked slowing of the pulse. This occurs most frequently in head operations in the semiupright posture. Change of position to the horizontal or slight Trendelenburg usually restores pressure and pulse rate almost immediately. The Trendelenburg posture is followed by an almost immediate drop in pressure, though not an alarming curve, and a rather prompt return to the individual level. H. G. Giddings (Trans. Amer. Assoc. of Anesthetists, Jour. Amer. Med. Assoc., July 6, 1918).

Alcohol.—In small amounts there is but little effect on pressure, but in any quantity there is a vasodilation and fall in pressure. Long-continued use leads to sclerotic changes and higher tension.

Tobacco.—Its moderate or occasional use produces a slight rise. When used to excess it produces low tension, due to the toxins in the tobacco.

Tea and Coffee.—Both produce a transitory rise. Subjects who indulge

freely often have a high tension, which leads to arteriosclerosis.

Treatment of Hypotension. — 1.

General hygiene and tonics.

2. Hydrotherapy is of some value, *e.g.*, needle bath, graduated from warm to cold; Vichy bath.

3. Massage.

4. Exercise when moderate and graduated to the needs of the individual.

5. Laxatives are of benefit where low tension is associated with constipation.

Report of a clinical study of blood-pressure in wound conditions. Pressure readings shortly after injury fell into 2 distinct groups: (1) hypertension, in which the systolic pressure varied from 150 to 160, or even 170 mm.; (2) hypotension, with primary shock and a pressure varying from 40 to 90 mm. At the first examination practically none showed a normal pressure.

As to treatment of shock, the best results, even in the severest cases with hemorrhage, were obtained by direct **blood transfusion**. Injections of **calcium hypertonic gum solution** produced an immediate rise in hemorrhage cases or cases of hypotension complicated by toxemia. This sometimes tided the patient through an operation. **Infusion with hypertonic saline** proved useful in milder cases of shock and hemorrhage. Results from infusion with physiologic salt solution were unsatisfactory. A steadily rising or maintained high pressure proved a favorable prognostic sign. A sudden fall may indicate onset of gas gangrene or sepsis. Fraser and Cowell (Jour. Amer. Med. Assoc., lxx, 520, 1918).

In 21 cases of hemorrhage in soldiers, the writers made blood volume determinations by the vital red method of Keith, Rowntree, and Geraghty. In 1 instance there was a reduction in the total blood bulk

to 54 per cent. Patients suffering from acute blood loss and diminished volume showed a much reduced pulse pressure, to 20 mm. or less. Hemoglobin determinations made on blood from the ear and vein showed a noteworthy difference, which bears a relation to the blood-pressure, as the discrepancy diminishes as the pressure rises. O. H. Robertson (Jour. Exper. Med., Feb., 1919).

PERCIVAL NICHOLSON,
Ardmore, Penna.

BLOOD TRANSFUSION. See
VENESECTION.

BLOOD-VESSELS, DISEASES OF. See various diseases of this class: ANEURISM, ARTERIOSCLEROSIS, ETC., and VASCULAR SYSTEM, DISEASES OF.

BLOOD-VESSELS, INJURIES OF. See VASCULAR SYSTEM: INJURIES TO BLOOD-VESSELS.

BLOOD-VESSELS, TUMORS OF.—Vascular tumors; angiomas.

DEFINITION.—Under the general title of vascular tumors, only the blood-vessel tumors of *new* formation (neoplastic), originating essentially by proliferation of vascular walls or from a matrix of angioblasts, will be considered in this article. This definition excludes from this class of tumors all swellings caused by *dilatation* of pre-existing blood-vessels: aneurisms, and varicose veins.

VARIETIES.—Tumors originating from blood-vessels have been grouped according to the character of the affected tissue, the clinical peculiarities of the growth as to color, etc., or to their anatomic and histologic peculiarities—the last the most scientific and satisfactory classification (Borrmann's classification).

The writer reviews 50 cases of blood cysts in the neck from the literature. In 21 an operation was attempted. Such a cyst is characterized by its congenital nature, its location on the side or middle and inside of a neck, the soft and fluctuating consistency, the extreme compressibility, the rapid and pronounced changes in size and tension during muscular effort, and the extraction with a needle cannula of normal or altered venous blood.

Compression of the tumefaction reduced it completely in the case of a babe of 4 months. Evacuation of blood never induced complete obliteration. In some cases 5 Gm. (1¼ drams) a day of a 1 to 5 **iodine solution**, injected into the cavity, was followed by cure, but this method is too dangerous, Woerner's patient dying suddenly after the injection. **Total enucleation** was done in 23 cases. It seems advisable to ligate the afferent veins beforehand to minimize hemorrhage; likewise the efferent veins to ward off gas embolism. These ligatures need not be tied unless necessity arises. In cases with extensive adhesions, some have resected part of the cyst wall and painted what was left with phenol and alcohol, but total enucleation ensures a complete cure. Nasseti (Clinica Chirurgica, Oct. 31, 1917).

1. **Angiomata, or hemangiomata:** large blood-filled space lined with a single layer of endothelium, benign in character, probably growing through increase of the surrounding connective tissue and (non-malignant) proliferation of the endothelia.

(a) **Simple, or Capillary, Angioma.**—Synonyms: *Telangiectasis, angiotel-ectasia, angioma glomeruliforme, plexi-forme, nevus vascularis, or sanguineus; birthmark, 'mother's mark, fuermal, gefassmal, tache de feu.* Vascular nevi have been designated according to their color, shape and distribution.

Nævus vasculosus vinosus ("port-wine mark"), *nævus araneus, nævus prominens, nævus vasculosus tuberosus, mulberry, or strawberry, nevus; venous nevus, pulsating nevus, nævus unius lateris* (Bärensprung), *nævus linearis* (Unna).

Superficial capillary angiomata are usually limited to the papillary layers of the corium, rarely extending beyond the subcutaneous cellular tissue. The growth consists of dilated capillaries and small veins, separated by a variable quantity of connective tissue. It is always present at birth, but may be so faint in color and small in size as to cause it to be overlooked until it enlarges.

The writer protests against the prevailing belief that nevi are always congenital or appear in the first few months of life. He reports a number of cases in which the typical "birthmark" lesions developed only in adult life. Some persons appear to be born with a nevic tendency, *i.e.*, with potential nevi. These may not show themselves, in the absence of an exciting factor, but make their appearance if some influence arises which will bring to life the nevic predisposition, and induce a localization of the nevi. Thus, in 1 case a wound of the hip caused a capillary angioma to develop on the injured extremity. In a second, exposure of the arm to cold was followed by an extensive venous and capillary nevus. In a third, freezing of the left foot was followed after over 3 years by a dozen confluent angiomatous nevi on the dorsum of the foot and just above it, and of additional nevi higher up on the same limb. H. Gougerot (Paris méd., Aug. 31, 1918).

This type of angioma may be cutaneous or subcutaneous, the latter remaining concealed under the normal skin until this becomes stretched out and thinned, terminating in the su

taneous form or in a true cavernous angioma. In addition to its peripheral extension, the tumor may develop downward and inward, into the corium and connective tissue, leading to the clinical picture of elephantiasis telangiectatica.

Clinical Manifestations.—The condition manifests itself externally by one or more sharply outlined reddened spots of flattened elevations of variable size, with circular or ragged contours, and of the same consistence as the healthy parts. Superficial angiomas are frequently multiple, larger spots being surrounded by spattering of smaller ones. The color of the affected portions varies from pink to purplish, depending upon the superficial or deep situation of the vessels. The discoloration is generally not sharply outlined from the healthy tissue. The seat of predilection is in the skin and subcutaneous tissue, also the adjacent mucous membranes (lips, lids, cheeks). Simple hemangioma is occasionally found in adipose tissue, especially of the orbit; in the muscles, the mamma, in the bone, brain, and spinal cord. With the exception of the pleura, testes, cartilaginous tissue, and certain parts of the nervous system, there is said to be no portion of the human body in which these vascular tumors have not been observed (Mauclair and de Bovis). Although no portion of the body is entirely exempt, fully two-thirds of all these angiomas affect the skin of the face. According to Lexer, based upon the statistics of Trendelenburg, who collected 170 cases, the majority affects the cheeks and forehead, next in order the lips, the nose, the surroundings of the ear, and the eyelids. Weinlechner places

71 per cent. of all cases at the head, especially the face.

(b) **Cavernous Angioma.**—Synonyms: *Cavernoma*, *navus prominens*. Larger than a capillary angioma; it is characterized by irregular blood-spaces lined with endothelium and formed by a connective-tissue stroma containing elastic fibers, closely resembling the normal erectile tissues of the body, *e.g.*, penis, clitoris, etc. The blood-spaces freely communi-



Cavernous angioma of hand. Palmar aspect. (Author's collection.)

cate with each other and are nourished by their own arteries, which empty their blood into dilated veins. The growth may appear as a diffused, ill-defined mass, but more often as a circumscribed tumor, which may have a distinct capsule. The consistence or density of the growth varies with the size of the blood-spaces, the amount of stroma, and the possible formation of angioliths, or blood calculi. The blood contained within these spaces is the cause of the purple or dark-red color of the growth. Sometimes there is a more extensive purple discolora-

tion and thickening of the skin, with marked development of cavernous tissue in the subcutaneous or intermuscular connective tissue, which may lead to the formation of large tumors, with great deformity of the affected parts. A cavernous angioma may be sharply differentiated from the surrounding tissue or it may merge gradually into it. Increase in size takes place partly by expansion and partly by infiltration, new blood-spaces forming in the fibrous septa



Cavernous angioma of face of congenital nevoid origin. Removal by extirpation. (Author's collection.)

and at the periphery. The development may be steadily and slowly progressive or there may be periodical exacerbations. When a cavernoma has a distinct capsule, its growth may become spontaneously and permanently arrested. In other cases the retrogressive changes remain limited to individual segments of the tumor. Seen on cross-section, the structure of cavernous angioma reproduces the erectile tissue of the penis, whitish septa of variable thickness bounding the communicating blood-spaces. These septa are formed of fibrous tissue and the remnants of

the tissue in which the cavernoma has developed (Billroth).

Clinical Manifestations.—Cavernous angiomata may appear in the form of small purple spots or of smooth or roughened purplish warts which project above the surface. Certain extreme cases of monstrous cavernomata are on record involving large areas of skin, the entire head, face, and extremities, but these possess less interest for the surgeon than for the pathologist. With special reference to their localization, cavernous angiomata most frequently affect the skin and the subcutaneous cellular tissue (cheeks, eyelids, lips, cranial coverings). When situated in the face they are apt to give rise to distressing deformities, and in the cranial coverings, to very severe pain, on account of the involvement of nerves (trigeminal branches).

Bibliography.—Franco: Contribution a l'etude des cavernomes congénitaux, *Archiv de Méd. Exp. et d'Anat. Pathol.*, May, 1906; Heide: Ein Fall von linksseitigen cavernösen Angiome, etc., *Archiv f. klin. Chir.*, vol. lxxx, H. 3, 1906; Trélat: *Gaz. Hebdomadaire*, 1874; Ashhurst, A. P. C.: Diffuse Cavernous Angioma of the Upper Extremities, *Annals of Surgery*, March, 1907.

(c) **Plexiform Angioma.**—Synonyms: *Cirroid aneurism*, *angioma arteriale racemosum* (Virchow), or *serpentinum*; *aneurisma per anastomosis seu anastomosen*; *tumeur erectile, cirsoide*; *vascular pulsating tumor*; *arteriectasia diffusa cirsoide*, *varix aneurismaticus congenitus*, *phlebarteriectasis*, *tumor vasculosus arterialis*.

Plexiform angiomata are more or less distinctly outlined tumors, developed from newly formed blood-vessels and occurring in definite arterial regions; usually (88 per cent.) originat-

ing from a congenital telangiectasis (nevi), more rarely in connection with traumatism (12 per cent., Fischer). The growth is made up of either arteries or veins, or of both arteries and veins in equal proportions. The arteries of the scalp and face are those most commonly affected, more rarely those of the extremities, the upper predominating (fingers, hand, and forearm). The

in the veins in the terminal stages. Plexiform angioma is most commonly derived from simple congenital angioma, and presumably develops upon congenital faulty development of a definite arterial area (Lexer). The trunks and branches at the seat of the process are involved up to the finest capillaries and ramifications, and the vessels of a lower grade become trans-



Circoid aneurism or aneurism by anastomosis. (Author's collection.)

growth may develop in pre-existing blood-vessels, due to an excessive formation of angioblasts in the vascular wall (Senn). The tortuous vessels present a parallel arrangement. New blood-vessels form as the tumor increases in size, which continue to communicate with the lumen of the altered vessel. The growing tumor involves the small and middle-sized arterial branches of the immediate surroundings, finally affecting the large trunks, which become dilated, lengthened, and twisted. Similar changes are observed

formed into specialized vessels. The condition, which has nothing in common with aneurism, represents a pathologic vascular proliferation, probably on a congenital basis, involving an entire arterial area, and consisting in the new formation of a network of hypertrophied and dilated arteries (Ziegler). The true neoplastic character of this form of angioma was first pointed out by Virchow.

Clinical Characterizations.—The skin covering a plexiform angioma is thinned out, discolored, and locally adherent,

forming a flattened tumor which gradually passes into the surroundings. It conveys to the touch the peculiar sensation of squirming fish bait, due to slipping away of individual vascular cords under the examining finger. Pulsation

in the head, on account of the large number of anastomoses. The atrophic skin covering may break down leaving obstinate ulcers with a tendency to hemorrhage and infection. Persistent, profuse, and often uncontrollable



Angioma racemosum. Side view. (*Carl Beck.*)
(*Annals of Surgery.*)

and bruit are usually well marked, the skin over the tumor vibrating synchronously with the heart-beat. Direct pressure upon the principal arteries causes a complete or partial evacuation of the tumor, with subsidence of the above phenomena when the growth is situated at the extremities; not so

hemorrhages lead to posthemorrhagic anemia and to death. Common clinical symptoms of plexiform angioma of the head are vertigo, pain, and functional disturbances due to infiltration of nerve cords and muscles. In general terms the clinical phenomena of plexiform angioma and arteriovenous aneurism

are identical because the lesions of the two conditions are analogous (arterio-venous anastomoses with arterialization and hypertrophy of veins). Another resemblance is a nutritional disturbance sometimes shown by an increase in size

l'Acad. de Méd., 1833, t. iii, H. 101; Burci: *Contributo all studio dell'aneurisma circoide*, *La Clinica Moderna*, January 3, 1906; Simmonds: *Ueber Angiomaracemosum und Serpentinum des Gehirns*, *Virchow's Arch.*, vol. clxxx, 1905; Fischer, F.: *Das arterielle*



Lines of ligation and incision. Four weeks after extirpation. (Carl Beck.) (*Annals of Surgery.*)

of the bones, the muscles, the skin and its appendages; in fact, no substantial difference between plexiform angioma and arteriovenous aneurism is recognized by some observers (Burci). The pathogeny, however, is essentially different.

Bibliography. — Breschet, G.: *Mémoires sur les anévrysmes* *Mém. de*

Rankenangioma (*Angioma arteriale racemosum*), *Deut. Chir.*, Leif 242, 1901; Verrou: *Anévrysme circoide de la région pariétale gauche*, *Bull. et Mém. de la Soc. de Chir.*, No. 29, 1902; Froelich: *Ein Fall von Rankenangioma der unt. Extremität*, *Dissers.*, Breslau, 1902; Coley: *Cirroid Aneurism Successfully Treated by Excision*, *Annals of Surgery*, September, 1901; Cloquet, Jules: *Pathol. Chirurg.*, Paris, 1831;

Virchow: *Die krankhaften Geschwülste*, vol. iii, 423; Petit, T. L.: *Oeuvres chirurg.*, 1740, t. i, Fig. 248; Bell, T.: *The Principles of Surgery*, London, 1826, vol. iii; Pelletan: *Clinique Chirurg.*, 1810, Fig. 59; Dupuytren: *Leçons orales*, Paris, 1839, t. iii, Fig. 43.

GENERAL HISTOLOGY.—The structure of angioma varies from independent vessels with distinct walls (simple angioma) to a true areolar tissue resembling erectile organs (cavernous angioma, *tumeur erectile* of Broca). Simple vascular tumors contain an abnormal number of large and otherwise altered capillaries and veins within a tissue normally belonging to the body. The new blood-vessels which constitute the growth are formed by budding of atypical angioblasts, the progressive tissue proliferation resulting in the formation of the tumor tissue proper. The endothelial lining of the vascular spaces—capillary, venous, or arterial—is the product of the angioblasts, a modified form of fibroblasts. Active proliferation follows in the other elements of the vascular wall, terminating in the formation of the outer and middle coats of the new vessels from connective-tissue and muscular constituents of the pre-existing vessels. While the constantly forming new blood-spaces establish communications with the older vascular spaces, the tumor as a whole remains sharply circumscribed from the surrounding tissue. The vascular walls contain flattened or cuboid endothelial cells and connective tissue in a circular arrangement. Growth takes place by the extension of vascular buds into their surroundings, the adjacent tissue becoming completely infiltrated by the constant new formation and dilatation of capillaries. While this manner of growth has the infiltrating character of malignant neoplasms, de-

stroying the affected parts inclusive of bone, metastasis of angiomatous tumors has never been observed, and there is no tendency to recurrence after complete removal. The increase in size is alternately slow and rapid, sometimes interrupted by long intervals, or permanently arrested at some stage of growth. The principal seat of angiomata is in the papillary layers of the corium, but the entire corium as well as the hypoderm may be involved. There often is a more or less well-marked increase of connective tissue in the surrounding of the vessels, and in extreme cases no tissue remains exempt. All vascular growths communicate very freely with blood-vessels (Senn).

In some capillary angiomata the process is chiefly or wholly limited to the arterial capillaries, while in others the veins are especially involved (venous nevi; venous angiomata). The more the external capillary budding predominates, the more rapidly does the angioma extend in all directions; the more the interstitial endothelial proliferation, the more does the tumor tend to encapsulation and remain stationary (Unna). Telangiectatic tumors, as a rule, are not sharply circumscribed, but have a tendency to extend in various directions into the surroundings. Their vessels are more independent than the blood-spaces of cavernomata, which are held together without a true wall by the intervacular connective tissue, an essential part of the entire structure. Cavernous angiomata of the skin are made up of an area of enlarged blood-vessels which is sharply differentiated from the subepithelial tissue on the one hand and the deeper corium on the other. The arterial wall of these vessels consists only of endothelium directly applied

to the surrounding connective tissue, which shows a circular arrangement. This tissue is more or less strongly developed and not of the same width throughout, so that small groups of vascular segments may be divided by dense connective-tissue septa from other similar groups. In this manner the angioma is divided into individual lobes. When development is active, the vessels are small as compared with the width of the intervening connective-tissue septa, but subsequently this disparity is reversed. The connective-tissue substance itself is usually poor in cells, but numerous nuclei are occasionally met with. It passes over into the corium, surrounding the neoplasm in such a way that there is no actual and distinct boundary. The plexus of blood-filled channels gives the impression, however, of an independent and separate structure. There is no transition to the vessels of the neighborhood and no indication of a transformation of the lumina into capillaries or *vice versa*.

Bibliography. — Lowenbach: A Contribution to the Histogenesis of Soft Nevi, *Virchow's Arch.*, vol. clvii, 1899; Lexer: *Das Angiom. Lehrb. d. allg. Chir.*, vol. ii, chap. v; Unna: *Die Histopathologie der Hautkrankheiten*, 1894; Stelwagon: *Treatise on Diseases of the Skin*, Phila. and London, 1905; Ziegler: *Lehrb. d. allg. Pathologie u. d. pathol. Anatomie*, xi, ed. 1905-6; Besnier, Brocq, et Jacquet: *La Pratique Dermatol.*, Paris, 1900; Senn: *Pathology and Surgical Treatment of Tumors*, 1895.

Histologic Affinities, Combinations with Other Growths, General Complications.—Upon this basis of histologic relationship, combinations with other tumor tissue have been observed to occur, especially as *angiolipomata* and *angiofibromata*. These tumors consist anatomically of a basis of adi-

pose tissue, connective tissue, or muscle tissue, and may be highly vascularized by extensive canalization with blood-vessels. Cystic transformation is also met with. A fatty change takes place by infiltration of the angioma with adipose tissue. Certain congenital lipomata are probably in reality degenerated vascular tumors. It must be admitted, on the other hand, that fat-tissue furnishes a favorable soil for the evolution of the angiomatous process. A simple hemangioma is not infrequently transformed into a cavernous angioma, especially in adipose tissue, the dilated capillaries forming a great cavernous system, with gradual atrophy and rupture of the interstitial tissue. Fibrous transformation is probably, as a rule, the result of interstitial inflammation between the capillaries, either due to external irritation or altered nutritional conditions of the connective-tissue elements. Spontaneous cure may occur as the result of contraction of scar-tissue and obliteration of the vessels. Cystic changes are not uncommon and have been accounted for by the separation of a vascular segment, which subsequently becomes dilated. It is less probable that cysts formed outside the vessels enter into communication with the vessels after giving way of the cyst-wall. The surface of these cysts is lined with endothelium, and their contents consist either of a hemorrhagic or a serous fluid.

Transition forms of hemangioendotheliomata occur as the result of transformation of vessels into narrow blood-filled tubes with thickened walls or into solid endothelial cords (collapsed vessels). There is a close relationship between angioma and en-

dothelioma, the cellular elements, of the former having the characteristic shape and arrangement of the parent soil (Senn). A cavernous angioma occasionally undergoes a parietal hypertrophy, the flattened endothelia becoming transformed into cuboid and cylindric cells (hypertrophic cavernous angioma or vascular endothelioma). In other cases, nests of large cells take the place of the blood through marked development and increase of the endothelia (hemangioid endothelioma, Ziegler). Vascular tumors are subject to hyaline and colloid degeneration, and to calculus formation resembling the phleboliths of varicose veins. Septic thrombophlebitis may occur as a complication of inflammation induced for curative purposes. Obliteration of all the blood-vessels may take place through extensive thrombosis, or the further growth of the angioma may be arrested by calcification of the stroma and of the vascular walls. Angioma of the superficial capillary type has been known to become transformed into a plexiform angioma or a sarcoma. Malignant neoplasms starting from dilated veins and formed from them by the development of new vessels are of very exceptional occurrence. The telangiectatic transformation of a malignant neoplasm must not be mistaken for cancerous change of a vascular growth. On the other hand, cavernous tissue not infrequently develops within the various tumors of the connective-tissue group.

Devic and Tolot, in reporting a carefully studied case of angiosarcoma of the membranes of the cord with coincident multiple angiomata of the spleen, left Eustachian tube, the mediastinum, and celluloadipose

capsule of the left kidney, discuss the question of the possible transformation or malignant degeneration of angiomata. Their researches in the literature would seem to show that apart from this observation (and this case is doubtful) no cases have been reported which demonstrate conclusively that an angioma can be evolved into a carcinoma, though a carcinoma may become telangiectatic. An epithelioma or carcinoma of the skin or elsewhere may be grafted into a nevus and ultimately blend with it, but the angiomatous tissue cannot be *transformed* into an epithelial neoplasm. The authors agree with Cornil and Ranvier that an angioma may become sarcomatous, or *vice versa*, as these are tissues of the same blastodermic derivation.

Bibliography.—Borchard: A Case of Angiosarcoma, Arch. f. klin. Chir., vol. lxxx, II. 3, 1906; Devic and Tolot, Rev. de méd., iii, 1906.

ETIOLOGY AND PATHOGENESIS.—

It is generally agreed that the vast majority of these growths are congenital and, with the exception of the traumatic angiomata developing in cicatrices and after injuries, the senile and other acquired types owe their origin to developmental disorders or defects in prenatal life. The vast majority appear at birth or shortly after. Of 558 cases, 500 appear in children under 12 months of age; 50, between 2 and 3 years, and only 8 between 4 and 15 years (Parker). Of 142 children treated in the Zurich clinic the congenital existence of angiomata was demonstrated in 82, and their appearance, a few days or weeks after birth, in 60 (Kraemer). *Sex*.—Statistics agree in giving the female sex a preponderating influence

(62 per cent. girls, Porta and Lebert); 365 girls to 172 boys (Parker); twice as many girls as boys in Gessler's collection of 1265 cases, and 71.4 per cent. girls in the Zurich clinic (Kraemer). For esthetic reasons it is probable that girls are often brought to the surgeon for treatment when the same condition is neglected in boys. It is statistically proved (Kraemer) that girls are brought to treatment at an earlier age than boys. A large number of the blemishes disappear after birth. Depaul claimed, with great authority, that fully one-third of the children born at the Clinique Obstetricale of the Faculté, Paris, showed nevi, which disappeared, in many, a few days or weeks after birth. *Heredity* undoubtedly plays an important part in the transmission of these defects, though to a much less extent than was at one time attributed to this influence (16 per cent., Kraemer).

In describing 3 cases the writer refers to other families occurring in the literature, stating that his series is the first to be recorded in Scandinavian medical literature. He considers the hereditary disposition towards the development of multiple telangiectases to be of a degenerative nature, in which toxic factors, especially alcohol, may play an important part. A description of the microscopical appearance of the lesions is given. E. Gjessing (Hospitalstidende, Nov. 10-17, 1915).

Three cases of this remarkable condition occurring in 3 generations of 1 family. The principal symptoms were epistaxis and occasional bleeding from the lips, gums or even from the skin. The bleeding always took place from small nevi. These nevi were usually round red spots, about the size of a pinhead, though occasionally the familiar "spider" forms were met with. They were situated chiefly on the cheeks, the skin of the

nose, ears and on the mucous membrane of the lips, nasal septum, hard palate, tongue and pharynx. A few spots were also observed on the hands and about the shoulders. Hutchinson and Oliver (Quart. Jour. of Med., Jan., 1916).

The writer observed hereditary hemorrhagic telangiectasia in 2 families, a condition made a clinical entity by Rendu. It attacks both sexes equally, and is transmitted alike by both. Twenty families have been recorded. In one of the author's cases the syndrome was traced through 5 generations. W. Steiner (Amer. Climat. and Clin. Soc.; Med. Rec., Oct. 7, 1916).

The *pathogenic theories* which have been suggested to account for the origin of these growths are innumerable and, even now, their mode of origin in the skin and tissues is problematic and highly debatable. Their great frequency in the most conspicuous parts of the body (face and head), and their disfiguring effect upon the countenance, has invested them with a special interest to the masses from the remotest antiquity to the present time. At first attributed to supernatural influences,—the expression of divine anger,—popular tradition, confirmed by professional opinion, gradually transferred their causation from divine wrath to the influence of emotional impressions of the mother on the unborn child. "Maternal impression" expresses a conviction, which is preserved in the name "mother's mark," which clings to the lay mind with unshakable tenacity and, to some extent, in a disguised form, in that of many contemporary medical observers. Discarding the antiquated theories which have had their day and are now buried with past generations, we will briefly mention a few which are acceptable to modern teaching and pathology.

I. *Localized disorders in the nutrition of pre-existing vessels leading to progressive hyperplasia* (Virchow) or regression to the embryonal type with neovascular formation. Virchow pointed out the existence of both an active and a passive process in the evolution of these tumors and showed that cavernous angioma originated through the dilatation of pre-existing vessels, both old and new, the vascular walls being thinned out by dilatation and gradually undergoing absorption. According to Journiac, the vessel walls become gradually softened and united with each other as the result of embryonic proliferation in the pre-existing vascular endothelium. This mode of formation appears most probable in the acquired angiomas—especially the cavernous and cirroid—in which traumatism and infection are the exciting causes (“vascularitis,” Coulon), as illustrated by Reverdin’s, Klippel and Trenau-nay’s, and other cases.

II. *Independent neovascular formation of migratory embryonal buds detached from germinal areas and leading an independent existence.* Ribbert, with whose name this application of Cohnheim’s theory is especially associated, after demonstrating (by injection) the circulatory independence of the angiomas and their relative isolation from the surrounding vessels, supports this view by the frequency with which nevi appear on the face and head (cheeks, lips, eyelids, and root of nose), where the branchial clefts existed, thus favoring the sequestration of highly vascular germinal tissue. In a modified way this is an application of Virchow’s explanation of the fissural angiomas, which bear the same relation to the branchial clefts. “A very slight irritative condition at the borders of the fissures, which are very abundantly supplied with vessels, is sufficient to induce a great vascular development which might possibly be recognized as a nevus, but which remains latent and only later becomes manifest” (Virchow). Thus, according to this theory (recently revived by Lamy), there are, “angiomas of the frontal germinal area,” of the “superior maxillary area,” of the “inferior maxillary area,” and those of the “second branchial arch.” This interpretation according to germinal areas is confirmed to some extent by the analogy which angiomas present with other congenital malformations in the same regions (inter-

maxillary clefts, branchial cysts, fistulæ, and tumors).

III. *Influence of physical or mechanical surface pressure on the fetus*—“intra-uterine pressure theory of Unna.” This theory strives to account for the fact that nevi appear usually in regions which are most likely to suffer from pressure during prenatal existence. For example, an extraordinary proportion of individuals, according to Unna, have nevi in the neighborhood of the occipital fontanelle, hidden by the hair in adults (35 per cent. of newborn infants, though only traces remain in adult life—10 to 20 per cent.—Politzer). Pressure would cause a localized compression anemia, followed by a paralytic hyperemia and ultimately a nevus formation. The vasomotor phase of this theory gives it some affinities to the “vascular theory,” expounded with considerable ingenuity by Trelat and Monod (1869), and supported by the great authority of Barwell. These authors argued for a localized vasomotor paralysis in embryonic life from central lesions followed by hypertrophy of the vessels and the surrounding tissues.

IV. Of all the theories propounded, that which at present appears the most attractive is the “*neural theory*,” originally foreshadowed by Royer (1835), Arndt (1839), and more clearly stated by Bärensprung, in 1863, when he reported 4 cases of *nevus unius lateralis*, and called attention to the topographic distribution of the nevi in segmentally innervated cutaneous areas. He attributed this systematic distribution to a prenatal injury or disease of the spinal ganglia, basing his belief upon: (1) The affection is unilateral and is accurately bounded by the median line; (2) the distribution corresponds to the peripheral expansion of one or more spinal nerves; (3) the cutaneous changes consist in hypertrophy of the elements in which terminate the peripheral nerves, namely, the cutaneous papillæ—glands, hair-follicles, etc., not participating in the lesion. He also called attention to the similarity of zona to nevus in its paraneural skin distribution. While Bärensprung’s observations were very favorably received, other observers (Phillipson, Petersen, Galewki) reported other cases in which the nevi appear to be related to Voigt’s lines, which define the zone of separation between

the functional spheres of two adjacent cutaneous nerves. In this way they attached the appearance of the nevus to symmetric *vascular*, rather than peripheral, nerve lines. While a number of cases seem to conform to these lines of demarcation, this disposition along Voigt's lines is far from constant. Other observers (Pitres and Vaillard) also attempted to modify the "neural theory" by associating the nevus formation with *peripheral trophic disturbances in the cutaneous nerves*. Subsequently, further inquiry into the neural distribution of zona (Brissaud) led to the expansion of the ganglionic theory of Bärensprung, into the spinal *neuron* or "*metameric theory*," by which the prenatal lesion was transferred from the spinal root ganglia to the cord itself. The distribution of the nevi in definite dermatomeres, corresponding to definite spinal segments or neuromeres, a view ably advocated by Lelong, has met some of the objections to Bärensprung's original views and gained for the neural theory many adherents.

In an interesting case reported with great care by Heide (Copenhagen), a large, diffuse cavernous angioma of the left lower extremity associated with extensive varices and pachydermia (elephantiasis teleangiectodes), he remarked that the metameric distribution of these lesions had been observed in connection with small groups of cutaneous nevi only, or in a few instances of large telangiectases in the skin, but not in extensive cavernomata. However, the skin areas affected in Heide's patient were found to conform exactly to the cutaneous distribution of the branches of the sacral plexus, while those innervated by the lumbar plexus remained intact.

Dr. Harvey Cushing, in a very thoughtful contribution, also reports 3 cases of nevi occurring in the distribution of the trigeminus, which he found associated with a similar condition of vascularity in the dura—also supplied by the same nerve. His observations support Bärensprung's ganglionic theory, which presupposes a prenatal lesion of the Gasserian ganglion caused by infection or injury.—R. MATAS.]

While the topographic distribution of some nevi and other surface angiomas is satisfactorily explained by the neurometameric theory, the mechan-

ism by which the nerve lesions cause the vascular ectasis and the correlated histologic disturbances still remains unaccounted for.

Klippel and Trenaunay (1900), in an admirable review of the subject, conclude that the rôle of the nervous system is secondary. It merely prepares the soil for infection by diminishing the local resistance, and thus prepares the way for the localization of the infectious or toxic agents in the blood-vessels, where they act as the exciting cause of the abnormal growths. In this they accept the views of Coulon in accounting for the acquired traumatic angiomas of post-natal life (see cases reported by Reverdin, Mauclair and De Bovis, Duplay and Cazin, and others) by infection in the blood-vessels themselves.

Again, in confirmation of the influence of the nervous system in the genesis of vascular growths the remarkable class of tumors grouped by Klippel and Trenaunay, under the title of "*osteohypertrophic varicose nevus of the extremities*" (previously described in the literature as "partial unilateral hypertrophy of the extremities" and under other titles), is well worthy of attention. This complex form of angiomatous disease is characterized by (1) a nevus involving the entire lower extremity, having a metameric distribution; (2) premature varicose veins limited to the diseased side exclusively and dating from childhood, if not from birth; (3) hypertrophy affecting all tissues of the diseased side, but especially the skeleton, which is increased in all dimensions—in length, width, and thickness. The disease is associated with certain other local, trophic, and nervous dis-

turbances, which may, however, be regarded as accessory. The entire triad of symptoms and manifestations are attributed to a common origin, probably a central metameric or trophic lesion of the cord, associated with infection localized in the peripheral vessels of the affected extremity and occurring as a prenatal disease.

DISTRIBUTION.—(a) **Skin and Deep Connective Tissue.**—Capillary or surface angiomas, as the name implies, are situated in the skin, preferably on the face and mouth, but sometimes extend over an entire side of the face or even one-half of the body. Cavernous and plexiform angiomas occupy the deep connective tissue, which is the primary seat of the growth in a number of cases, or this may be involved by extension from the skin. In the former case, the skin covering of the tumor generally presents a healthy appearance, unless the skin becomes atrophic and ulcerated as the result of pressure, malnutrition, or traumatism. In rare cases, simple angiomas are found in adipose tissue, especially in the orbit.

(b) **Skin and Mucous Surfaces.**—Angiomas of the mucosæ are of rare occurrence, and very few cases are on record where the growth presented in other mucous membranes than those of the tongue and the rectum. Involvement of the mucosa by extension from the skin is more common. Next to, in, and under the skin, simple angiomas are found with especial frequency in the adjacent mucous membranes (lips, lids, cheeks). The cause seems to be a dilatation of the capillary vessels in the delicate network of the subepithelial layer.

(c) **Muscular System.**—Primary

angiomas of the muscles are growths which develop from the vascular plexus of a voluntary muscle, or in the perimysium between the muscle-fibers. They may be either simple (rare) or cavernous in type. The arrangement of the vessels in these cavernous angiomas of muscles is extremely variable. Although veins are found more rarely than arteries, they are not entirely absent. When present in considerable numbers, the lumen of the vessels is much enlarged, and in certain cases this venous dilatation seems to have constituted the first phase of the cavity. The capillaries are the most important element in this connection, giving rise to simple angioma not only, but resulting by marked dilatation and fusion in the blood-spaces of cavernous angiomas. With special reference to the pathogenesis, the origin of these growths has been referred to a congenital malformation of the vessels, which does not manifest itself until an advanced age of the individual (Sutter). The existence of a faulty congenital disposition of a circumscribed tissue area has been responsible (Ribbert, Riethus). Increase of the interstitial connective tissue and the adipose tissue in the muscle has been regarded as the primary change, followed by the development of capillary vessels and terminating in atrophy of the connective tissue, with ultimate production of a cavernous space (Pupovac). A history of traumatism is given in too many cases to be regarded as merely accidental. The growth is rarely larger than an orange, and the increase in size is very gradual. The surface of these tumors is lobulated, and they vary as to size and consist-

ency, being usually doughy to the touch and sometimes pulsating.

They may present as mixed tumors, with lymphangiomata or lipomata (fibrolipangioma). A cavernous tumor of the semimembranosus surrounded by a lipomatous mass was reported by Keller, who found 22 corresponding cases in the literature (compiled by Alessandri). A case of fibromyangioma characterized by marked proliferation of non-striated muscle in a peripheral muscle was reported by Honsell. An extremely rare, perhaps unique, case of cavernous angioma situated in the intermuscular adipose tissue, between the serratus anterior and the latissimus dorsi, was recently observed by Kuttner. This tumor could not be classified as a true muscular angioma, on account of the intact condition of the skin, the subcutaneous cellular tissue, and the muscle, and also the absence of any connection of the tumor with the deeper layers.

While primary angiomata of voluntary muscle are relatively rare, it is not at all uncommon for a cutaneous angioma to extend to the subjacent tissues, sometimes involving the muscles to a very considerable extent. The character of muscular angiomata appears to be benign in the majority of cases, but diffuse infiltrating growths always imply a potential malignancy. The rate of growth is very slow, sometimes extending over fifteen to twenty years. There may be no other than mechanical symptoms, while certain cases are characterized by severe pain, due to compression of large nerves by the growth, especially when this is situated at the extremities. The symptoms and diagnosis of these

growths will be referred to again under general diagnosis of angiomata. No other than surgical treatment enters into consideration, and, on account of the usually diffuse distribution of the growths in the muscle, operative interference, as a rule, will have to consist in extirpation of the entire affected muscle or muscle segment.

Bibliography for Angiomata of the Muscles.—Reclus et Magitot: Sur deux cas d'angiomes primitifs des muscles striés, *Revue de Chir.*, vol. lxxxviii, 1906; Howell: *Beit. zur klin. Chir.*, vol. xxxii, 1902; Rigaud: Thèse de Paris, 1903; Eve, Frederick: *Brit. Med. Jour.*, May 16, 1903; Bajardi: *Clin. Med.*, Florence, 1900; Pupovac: *Arch. f. klin. Chir.*, vol. liv, 1897; Riethus: *Beit. z. klin. Chir.*, vol. xlii, 1904; Keller: *Zur Kazuistik und Histologie der Kavernosen Muskelangioome*, *Deut. Zeit. f. Chir.*, vol. lxxiv, 1904; Alessandri: Un caso di angioma cavernoso del muscolo trapezio; *Policlinico*, Sez. Chir., No. 3, 1904; Margarucci: Sull' angioma primitivo dei muscoli volontari; *Policlinico*, Sez. Chir., No. 12, 1902; Billroth: *Gurtl's Jahresb. für 1863-65*.

(d) **Osseous System.**—Angiomata in bone (myelogenous angioma of Virchow) are of extremely infrequent occurrence. They are invariably produced by the formation of new blood-vessels from a matrix of angioblasts (Senn). The resemblance to osteosarcoma, a relatively very common affection, is so great as to render a positive *intravital* diagnosis impossible. Pulsation is sometimes present, due to the great vascularity of these growths, and has led to the erroneous diagnosis of bone-aneurism. The long bones are the seat of predilection of vascular tumors of the osseous system; usually near the articular or epiphyseal extremity of the bone,

where the vascular distribution is greatest. Of 23 cases of endothelioma and perithelioma collected by Howard and Crile, the humerus was affected 5 times; the ulna once; the iliac bones once; the femur 4 times; the head 3 times; the vertebral column twice; the sternum and ribs once; other bones 3 times.

Bibliography.—Howard and Crile: Endothelioma and Perithelioma of Bone, *Annals of Surgery*, 1905; Verneuil: *Bull. de la Soc. Anat.*, 1847, quoted by Broca; Senn, N.: *The Pathology and Surgical Treatment of Tumors*, Philadelphia, 1895.

Parasynovial angioma occurring in the knee-joint has been observed in 2 instances. In Martel's case the growth was not directly associated with the venous system, but connected with the arterial system, and constituted a plexiform angioma.

Bibliography.—Martel: Angiomes Cavernaux Parasynoviaux, *Gaz. des Hôp.*, No. 116, 1898; Zesas: Ueber eine Seltene Geschwulst (Angioma Cav.) der Kniegelenks Kaps. *Deutsch. Zeitsch. f. Chir.*, vol. lxxxii, 1906.

TOPOGRAPHIC DISTRIBUTION.—Of all forms of angioma, including the ordinary mother's mark, the usual localization is in the head and the least frequent in the limbs, as may be seen from the following table compiled by Ashlurst from Kraemer and Gessler:—

Head and Neck, 57 per cent. (Kraemer); 79 per cent. (Gessler).

Trunk, 28 per cent. (Kraemer); 11 per cent. (Gessler).

Extremities, 12.5 per cent. (Kraemer); 9 per cent. (Gessler).

Head.—*Intracranial* angiomata may belong to blood-cysts of bone developed from the nutrient vessels of the parietal bone. The cysts are

lined with endothelial cells, and their origin is referred to the angioblasts (Senn). *Meningeal* angiomata take their origin from the vessels of the pia mater, and have been found in the fourth ventricle and upon the surface of the middle lobe. Plexiform angioma of the brain is very rare. Simmonds collected 5 cases.

Scalp.—Simple angiomata of the soft cranial coverings, according to Heinecke, constitute 33 per cent. of the angiomata of the head. Cavernous angioma of the skull is apt to infiltrate the bone, communicating with the large blood channels through dilated capillaries and veins. Their intimate connection with nerves, especially trigeminal branches, may give rise to severe pain. Plexiform angioma preferably affects the arteries of the scalp and face.

Forehead.—This is the favorite seat of simple angioma, especially in the region of the glabella, at the inner end of the eyebrow, and over the fontanelles. Of 109 angiomatous tumors of the skull compiled by Heinecke, 38 were situated on the forehead. A typical case was reported by Berndt, the patient making a good recovery after extirpation of the tumor and ligation of the veins supplying it. Of 19 cases of arterial nevi collected by Vincent, 17 were situated exclusively in the head. They are not infrequently multiple, their number ranging approximately from 2 to 8, and may be the forerunners of plexiform angioma.

Conjunctiva.—Angiomata of the conjunctiva are very uncommon. Only 2 cases were observed in the course of twenty-eight years in an institution having an unusual polyclinic material of 8000 to 9000 patients.

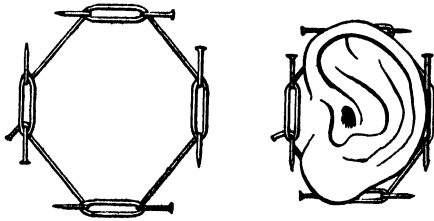
(Fehr). According to Virchow, angiomas of the conjunctiva represent either an extension of palpebral tumors, or they may develop primarily in the conjunctiva. The latter form is especially rare and hardly ever progresses beyond the nevus stage. In the majority of cases these growths are congenital or develop within the first few years of life (Saemisch). Their favorite seat is the internal commissure, especially the semilunar fold. They may remain latent during years and then gradually increase in volume, giving rise to disturbances, by increasing the tension of the conjunctival sac, until they finally protrude from the orbit. As in all angiomatous tumors, the diagnosis is based upon the color, form, consistency, enlargement, and manner of growth. Cavernous angiomas must be differentiated from highly vascularized lipomata and fibromata, which may simulate cavernous growths through excessive development of their blood-vessels. Of 17 cases of primary angioma of the conjunctiva observed by Fehr, 12 were of the cavernous type and 5 were telangiectatic. The growth in all these cases was very slow and superficial, these tumors being relatively benign. There was neither metastasis nor recurrence after radical operation, consisting in ligation of the tumor followed by excision.

Eye.—The bulb is endangered by progression to the orbit by angiomas of the eyelids, which may be involved primarily or by extension of the growth from the temporal and nasofrontal region. Cavernous angiomas sometimes originate in the orbit, and are either encapsulated or diffuse, resulting in displacement of the bulb.

The most important signs of cavernous orbital angioma are absence of pain, very slow growth, preserved motility of the eye, elastic consistency and compressibility of the tumor, and especially a tendency to swell under the influence of venous stasis. Pulsating exophthalmos, a pulsating tumor at the inner angle of the orbit with protrusion of the eyeball, has been observed as the result of distention of the dilated branches of the ophthalmic artery by a plexiform angioma. Angiomas of the choroid are rare. Six cases were compiled from the literature by Bossaline and Hallauer. Simple angioma is exceptionally met with in the adipose tissue of the orbit. Deep-seated angiomas of the orbit originate beneath the orbital aponeurosis in the celluloadipose tissue which surrounds the eyeball. They are, as a rule, arterial, pulsating, and infiltrating in character. Since the resistance of the bony orbital walls prevents their extension in all directions, they progress toward the front, either pushing the eyeball before them or passing above and, more rarely, below it. The eyelid is invariably raised up at an early stage of the growth. These orbital angiomas may acquire considerable size, stretching and thinning the bony walls and extending into the cranial cavity.

Upper Air Passages.—Vascular tumors are of relatively rare occurrence in this locality (Cobb, Kyle). With special reference to the nose, the frequency of these growths is not universally agreed upon. Jonathan Wright does not consider them to be as rare as commonly represented, mentioning about 30 cases from

American and German sources. In a total of 264 cases compiled by Schimmelpfennig, 113 were located in the nose and 151 in the mouth and pharynx. According to Kyle, these growths are more often found on the nasal septum than on the turbinates. A large number of so-called tumors of the nose are bleeding polypi of the nasal septum. Mucous polypi and growths of the posterior portion of the turbinates may simulate vascular tumors, but these present a peculiar purplish or dark-red discoloration. Moreover, they are of spongy con-



These cuts are intended to give a schematic representation of the author's method of elastic constriction with the aid of pins, used as binding posts, to secure local anesthesia and hemostasis in all operations on the auricle. This method was very successfully tried by the author in extirpating a gigantic cavernous angioma of the auricle (see illustrated article, *Medical News*, Philadelphia, December 24, 1892).

sistency and are readily reduced in size by pressure. Although almost invariably congenital, vascular tumors of the upper air passages generally manifest themselves at an advanced period of life. Of 135 of these patients, 61 were men and 74 were women. In the treatment of these conditions the galvanocautery and the hot snare have proved most valuable. Multiple telangiectases of the skin and mucosa of the nose and mouth were recently reported by Kelly.

Lips.—At the lips, simple vascular tumors may simulate the picture of macrocheilia, the result of lymphangioma. Under these conditions, the upper lip, which is the one generally affected, hangs down over the chin in shape of an irregularly outlined purplish welt, the lower tip protruding like a proboscis. The swelling enlarges by changes of position (stooping) and on exertion (crying) or excitement. Virchow refers to the lower lip of Emperor Leopold of Austria, which hung down to the chin when the monarch's ire was aroused.

Auricle.—Angioma of the auricle, almost invariably of congenital origin, is seen with especial frequency in children. In the majority of cases, the growth involves the adjacent region of the cheek. It may be plexiform and telangiectatic, which is usually the case in the vicinity of the tragus, whereas in the remaining portions of the auricle the angioma is more apt to be cavernous. The condition acquires clinical importance on account of the tendency to hemorrhage. When the tumor is arterial in character, distressing ear noises are often complained of as the result of pulsation. Auricular angioma has been reported to follow puncture of the lobe of the ear for so-called ornamental purposes. In regard to the treatment it may be stated that multiple galvanopuncture, although frequently followed by recurrence, is preferable to excision, except in cases in which the entire cartilage is involved, when the pinna is to be amputated. (The author's method of controlling the circulation of the ear, either for partial resection or total amputation is here exhibited.)

In total amputations for malignant disease involving the auditory canal in which *total* excision is required, the method is not applicable for obvious reasons.

The root of the auricle is first infiltrated to the periosteum of the mastoid with beta-eucaine (0.2 of 1 per cent.) and adrenalin sol. (1:1000, 1 per cent.) in physiological salt solution (0.8 per cent.), an infiltrated zone which edematizes the root of the concha and surrounding tissues like a drop-sical collar. The solution is forced into the tissues with the author's infiltrating pump. Four pins are then inserted at equidistant points, and a thin rubber band is wound around them several times in the manner shown in the diagram. As the elastic thread is wound around the root of the pinna, the ear becomes markedly pedunculated, and its outline more contracted and circular, the lobule being thrown up toward the helix.

Tongue.—Both simple and cavernous angiomata have been observed to occur in the tongue. Gibson reports an interesting case, in which the growth began in childhood as a black spot on the tongue, and sixteen years later extended over the floor of the mouth, the parotid gland, and the hard and soft palate. The treatment was conservative, in view of the probability of recurrence. Senn successfully removed an extensive vascular tumor of the tongue by excision.

Tonsils.—Vascular growths, limited and confined to the tonsil, are rarely met with. Hartmann found only 2 recorded cases of angioma varicosa of the tonsil, to which he adds a personal observation. The growths are best removed very slowly with the cold snare, to avoid hemorrhage.

Neck.—The upper triangle of the neck sometimes is the seat of vascular growths. In a case observed by Elliott, a cavernous angioma of the neck developed five years after the removal of a small submaxillary angioma. The largest vascular space

was situated in the center of the tumor and was about the size of a lemon. Numerous other smaller cavities were distributed through the substance of the growth. A number of tumors situated at the point of bifurcation of the carotid were described by Paltauf, who suggested for these growths the designation endo- (peri-) thelioma intercaroticum. Valuable contributions to the subject of carotid tumor have been recently made by Keen, Funke, and Da Costa. Certain angiomata of the *parotid* region seem to involve the gland as well as the muscles and all the soft parts of the cheek.

Breast.—The mammary gland may be the seat of angioma, but this location is infrequent. Nine undoubted cases from the literature were collected by Malapert and Morichau-Beauchant, with the addition of a personal observation. The tumor is usually present at birth or develops within the first few months of life. It may be cutaneous, subcutaneous, or glandular, developing in the celluloadipose stroma of the gland. The glandular elements become atrophied as the angioma progressively enlarges. The growth is generally diffuse, but sometimes there is a distinct capsule (Bajardi's case). All angiomata of the breast have a tendency to progression. They slowly increase in size, the growth sometimes becoming accelerated as the result of traumatism. In other cases they remain stationary during variable periods. Complications are uncommon, but may occur in the shape of hemorrhage due to ulceration of the skin invaded by the angiomatous process. The treatment varies with the character of the tumor. Super-

ficial nevi may be treated in the ordinary manner, while subcutaneous growths are best treated by excision, unless the gland is involved, when entire removal of the breast is indicated for the prevention of recurrence.

Case of angioma of the mammary gland in a 22-year-old girl, which had

tuating and to contain a chocolate-brown fluid. Microscopic examination showed that the tumor was encapsulated and that the interior was composed largely of blood-vessels with some connective tissue around the larger-sized vessels. The tumor was a congenital hemangioma into which hemorrhage had occurred apparently because of some external



Multiple cavernomata of upper extremity. Ventral and dorsal aspects.
(Courtesy of Dr O A Porter, Boston.)

been gradually increasing in size since childhood. The last three years it had become painful. No injury had been received so far as the patient knew. The tumor was located in the upper outer portion and in the depths of the left mammary gland. Upon palpation it seemed to be either a fibroadenoma or a cyst. The patient desired operation because of the pain which the condition produced. During the operation it was found that the tumor, which was about the size of a walnut, could not be shelled out. After it was removed it was found to be soft and to a slight extent fluc-

influence. Although the operation had been done three years before the case was reported, there had been no recurrence at that time. Carl (*Deut. Zeit. f. Chir.*, Bd. cxi, II. 1-3, 1912).

Upper Extremities.—Solitary angioma of the upper extremity is relatively frequent, whereas multiple vascular growths are uncommon, although instances have been reported by Virchow, Cruveilhier, Esmarch, Schuch, Gasne et Guillaïn, Abner Post, and others. Angioma of the entire upper extremity, extending from the

root of the neck to the finger-tips, in an adult male, was observed by Abbe. In the case reported by Gasne et Guillaïn (adult female) the vascular anomaly had existed from the time of birth, involving the right upper extremity and lateral thoracic region. In 12 cases of diffuse cavernous angioma of the extremities recently collected by Ashhurst, 10 involved the upper extremities.

Hand.—Congenital cavernomata are rare in the hand, but in many reports merely the upper extremity, in general, is mentioned as the seat of the growth. Next to the head, the hand is the seat of predilection of angioma, according to Kirmisson. Neither telangiectatic nor cavernous growths are uncommon at the hands and fingers. The majority of all digital tumors are simple or cavernous angioma (Koenig). In the remarkable case of cavernoma of the hand in a newborn child, recently reported by Franco, the right hand presented an irregular swelling nearly as large as the infant's head, involving the wrist, the carpus and metacarpus, and the first three fingers. In view of the monstrous development of the angioma and corresponding deformity, the treatment consisted in amputation of the forearm, which was readily tolerated and recovered from. The specimen was classified as a lipogenous cavernoma (Virchow), and its origin referred to the cellular adipose tissue. Angiokeratoma (telangiectatic and cornified nodules, Mibelli) is especially common in the hands (Rau).

Lower Extremities.—Only a small number of cases of plexiform angioma affecting the lower extremity are on record. Ten cases were compiled

from the literature by Froelich, 2 of which affected the gluteal region; 1 the patella; 3 the leg and foot; 3 the foot alone. The right and left sides were about equally represented. The reason for the rarity of the condition at the extremities as compared to the head lies in the fact that plexiform angioma frequently develops upon a telangiectatic base, which is most common in the head. Blood-pressure being much lower in the extremities than in the head, general hyperemia has a less marked effect. Moreover, the blood-supply to the extremities is physiologically less than to the head. The limb affected by plexiform angioma becomes swollen and markedly enlarged. It has been found to be from 2 to 3 cm. longer than on the normal side, and in 1 case the leg of the affected side was 5 cm. longer than the other. The treatment of these growths aims at the removal of the tumor as completely as possible and at the maintenance or restoration of function. Extirpation with or without previous ligation of the nutrient vessels of the tumor is the most rational and radical procedure, combining the greatest prospect of success with the smallest probability of recurrence. Partial excision is suitable for tumors too large to permit of complete removal. The risk involved in excision is hemorrhage, both primary and secondary.

A certain predilection for the lower extremities is shown by the very rare, diffuse, and extensive angiomatous formations known as *phlebogenous angioma* (Virchow). Presenting in the shape of multiple encapsulated tumors in the course of a large venous trunk, from whose vasa vasorum they seemed to originate,

these phlebogenous growths cannot be sharply differentiated from certain diffuse peripheral angiomas. Transition forms occur here as well as between any two other forms of angioma. A small independent group, not extensively represented in the literature, is characterized by the diffuse distribution and the tendency to invade the neighboring soft parts. The condition is well illustrated by a case recently observed by Heide, in which the left foot was affected, especially in the anterior portion, including the toes, the fibular side, and the sole of the foot.

The remarkable group of cases described under the title of Varicose (Osteohypertrophic Nevus, by Klippel and Trenaunay (see Etiology and Pathogeny), are peculiar to the lower extremities, involving one or both limbs. The case reported by J. Adams, Chassaignac, Trelat, and Monod, Duzea, Andry and Monan, Barwell, Duplay, and others collected by the authors mentioned, are remarkable illustrations of the localization in the lower extremities of this complex type of angioma.

Splanchnic, or Visceral, Angiomata.—*Liver.*—The most common seat of angiomata within the body is the liver, where they present in form of small foci which project slightly beyond the surface. They are of variable size, up to a few centimeters in diameter, and substitute the liver tissue. The growth is sharply differentiated from the surroundings by connective tissue. The origin is probably referable to a local disturbance of development, starting from the vessels of Glisson's capsule or from the interacinous capillaries. The process is characterized by an

abnormal vascular development and a simultaneous arrest of growth in the other tissue constituents. The increase in size of these tumors is very gradual and limited, and, as a rule, the liver-cells of the surroundings present no evidence of degeneration. The condition is most frequently discovered as accidental postmortem findings at the autopsy of aged individuals; but it is a remarkable fact that some of the largest specimens have been removed from children. The two largest hepatic angiomata operated upon occurred in adult women, 41 and 37 years of age, respectively (Rosenthal, Langer).

Keen, in his report of a case of angioma of the liver treated successfully by extraperitonealization and elastic ligature, reports 58 liver resections or operations for tumors from 1888 to 1897, compiled from the literature. Of these, 4 were angiomata, 1 cavernous, and 1 angiofibroma. These were nearly all treated by the elastic ligature of the pedicle outside of the abdominal cavity. It is probable that in future these and other tumors of the liver will become more amenable to direct intraperitoneal treatment, in view of the marked improvement in the technique of hepatic resection which has followed since the introduction of better methods of hemostasis by Kousnetzouff and Pensky, Cullen, Garré, and others (see section on Surgery of the Abdomen, Liver).

The lobulated structure of these growths in a general way resembles the structure of cutaneous cavernoma (Ribbert). The blood-spaces form various groups divided by septa into compartments of variable width which sometimes communicate with each

other. The width of the spaces and the thickness of the septa vary within very considerable limits. The inner wall is lined with endothelium, and smooth muscle-fibers are sometimes found in the wall of the vessel. A number of contradictory views have been expressed concerning the pathogenesis: "Failure of independent area to become incorporated into the liver in the typical manner" (Ribbert); "tissue malformation through faulty germinal predisposition" (Schmieden); "thickening of connective tissue with disappearance of vessels and subsequent atrophy of liver cells" (Rindfleisch and others). The stagnation theory, according to which proliferation of the vascular wall was caused secondarily by a local stagnation of the bile, has been practically discarded.

Spleen.—Altogether only about a dozen cases of cavernous tumors of the spleen are registered in the literature, including two observations upon animals. In the spleen the vascular spaces do not take the place of the missing parenchyma essential to the specific function of the organ; but the epithelial lining of the vascular spaces results in an increased physiologic function as compared to the normal splenic pulp. Important points in regard to the structure of the tumor are: the presence of vascular ducts in direct connection with the Malpighian corpuscles; the communication of the ducts with each other and with the cavities; the transition of ducts lined with high epithelium into venous capillaries lined with flattened endothelium; the formation of the parietal lining of the cavities by septa with a layer of flattened endothelium. A system of

canals in the spleen was described by Billroth and by Böhm, which essentially agrees with the characteristics of these cavernous vessels. Böhm says that the splenic pulp in man is composed of a canalicular system lined with typical epithelium, the canals being probably blood-capillaries of a peculiar structure. Billroth's capillary veins are assumed by Böhm to open into the Malpighian corpuscles. The various characteristic features are all reproduced in the cavernous ducts. According to Albrecht, the pathogenesis of cavernoma of the spleen is probably referable to a faulty predisposition of the local vascular apparatus (primary variation of Billroth's capillary veins).

Alimentary Canal.—Cavernous angiomas have been observed in this location, although with extreme rarity, in both children and adults. Approximately 20 cases are described in the literature. The growth usually occupies the stomach and esophagus or portions of the colon and small intestine. Fatal hemorrhage is apt to occur in those cases especially where the esophagus is the seat of the angioma; more particularly in children. In addition to the bowel, in a case described by Sommer, the bladder, the broad ligaments, the ovaries, and the retrovisceral cellular tissue of the abdomen participated in the growth. A case of multiple cavernous angiomas of the intestine was recently reported by McCallum. In another recent case, contributed by Bennecke, the cavernous phlebectases were distributed throughout the esophagus and the stomach, as well as the intestine. Metastasis has been observed in 1 case in the celiac ganglion.

The pathogenesis of these vascular

growths of the alimentary canal is not agreed upon, and four principal theories have been suggested: (1) Mechanical factors producing a rise of pressure in the portal vein (Orff). (2) Nervous influences injuring the power of resistance of the venous walls (not accepted). (3) Primary inflammatory changes in the venous walls (Lilie). (4) Primary malformation of the venous wall with imperfect development of the muscular and elastic constituents (Bennecke).

Mesentery.—A very unusual case of venous cavernous angioma of the mesentery, complicated by intestinal obstruction, is reported by Chas. Julliard, of Geneva (*Rev. de Gyn. et de Chir. Abd.*, 1904, p. 227). The author collected 78 cases of mesenteric tumors of all kinds and this is the only case of angioma reported. It was situated in the mesentery of the duodenum and caused acute intestinal obstruction, which ultimately proved fatal. The clinical, pathologic, and surgical bearings of this unique growth are thoroughly discussed by Julliard.

Ovary.—A very rare and probably unique case of angioma simplex is reported by Jacobsen, in the *Post Graduate*, London, No. 1, 1905. It formed on the surface of the right ovary of a woman, aged 35, who had borne 2 children. The tumor ruptured with fatal hemorrhage into the abdominal cavity.

Placenta.—Tumors characterized by the new formation of blood-vessels have been observed to occur in the placenta, representing the curious phenomenon of a new growth within a new growth. The various types under which this new formation of vessels may manifest itself were

described by Kraus, who classified certain tumors of the placenta as hemangiomata because the bulk of these growths was made up of blood-vessels. The connective-tissue elements were only increased to the extent required for the support and framework of the tumor substance. The condition consists essentially in the alteration of a circumscribed capillary area. The growth is sometimes encapsulated and may originate at any stage in the formation of the placenta.

The location of the tumor is in the chorionic villi and their ramifications. As a rule, the angioma endangers the life of the fetus through disturbance of the fetal circulation.

A large angioma in peritendon tissue of the forearm of a young piano teacher was successfully removed by the writer as also in a second similar case. He has found only 4 cases of the kind on record. There was no pulsation in any instance, but concretions in the angioma were common. The growth never involved the tendon but spread over a larger extent than is common with angiomas in muscle tissue. The angiomas were removed in all the cases on record except in Richet's case; he cured the boy of 10 by injection of **ferric chlorid** into the growth. Weil (*Beiträge z. klin. chir.*, lxxxviii, No. 1, 1914).

GENERAL DIAGNOSIS.—The characteristic appearance of simple nevi renders the diagnosis easy and positive in the majority of cases. They may occur in any portion of the body, but are relatively rare on the abdomen and thorax. The seat of predilection is the head, especially the face. In cavernous angioma, other important diagnostic features are the compressibility of the growth and its capacity to swell and become

turgid; hence, "erectile tumor." The tumor mass is soft and yielding, compression serving to diminish its size and lessen the discoloration. Upon removal of the pressure, the blood returns into the tumor and the former appearance is re-established. The tumor becomes noticeably larger by lowering and compressing the affected part. These various pressure changes are not obtainable when the growths contain calcified angioliths or much adipose tissue. If there is a communication with larger arterial vessels, pulsation may be added as another characteristic. A plexiform angioma is usually unmistakable on account of the tortuous and pulsating arteries, which can be readily palpated, and the irregularly outlined distribution of the neoplasm.

Circumscribed angiomatous growths in muscles are rarely larger than a nut or a hen's egg. The size of the tumor is not so readily determined when the distribution is diffuse. Since these muscular growths are absolutely independent of the skin, this is freely movable above them, a sign of considerable diagnostic importance. The consistence is variable, and they may be as hard and irreducible as fibromata. When the growth is felt to be very firm on pressure, it is sometimes found to contain calcareous concretions (angioliths), whose presence may assist the diagnosis, though more often they confuse it by suggesting osseous or chondroid functions, as in sarcoma. As a rule, however, they are somewhat doughy to the touch and sometimes apparently reducible, depending to a certain extent upon the relaxation or contraction of the affected muscle. The Esmarch band-

age applied to the root of the limb in certain cases determines a diminution, and in others an increase, in the volume of the tumor. The differential diagnosis from intermuscular sarcoma is sometimes very difficult, the slow course of angioma being the most important distinction. The diagnosis of vascular tumors of bone is impossible during life, on account of the close resemblance to osteosarcoma.

Circumscribed painful angioma is a variety of vascular tumor which is almost invariably situated in the extremities, especially the upper arm and forearm, but also the leg. The differential diagnosis from other painful tumors is based upon the rough and irregular surface, the bluish discoloration of the skin, and moderate dilatation of the subcutaneous veins in the surroundings. The growth is soft in the beginning and only becomes painful as the result of induration with pressure on the nerves. Broca describes a case observed by Verneuil (scaphoid bone of tarsus) which was particularly characterized by severe pain.

GENERAL PROGNOSIS.—Angiomata are benign in character, but their behavior is extremely variable. They may remain stationary or show a tendency to subsidence, while others suddenly start to grow, either spontaneously or as the result of traumatism. An obscure influence of pregnancy and menstruation has been noticed in this connection. Ulceration is not of common occurrence. In the absence of complications (inflammation, ulceration, hemorrhage, transformation into a plexiform angioma), simple superficial vascular growths have a very favorable prog-

nosis as far as health and life are concerned. A spontaneous cure sometimes results as the sequel to inflammatory changes. On the other hand, the prognosis must always be guarded as to the outcome of a given treatment when the growth is other than very small, circumscribed, and superficial. Left alone, simple vascular tumors usually persist in their original size and color, but there is a certain danger of transformation into plexiform angiomas. The danger of ulceration and hemorrhage is greatest in the tumors exposed to frequent contact and friction. The prognosis of cavernous and plexiform angiomas is more serious, on account of the tendency to inflammation of these tumors, with septic thrombophlebitis, pyemia, and death. Moreover, there is the risk of sudden and sometimes alarming increase in size, and in view of this possibility it is advisable to keep all these growths under observation for the purpose of timely interference should this become necessary. In general terms, the prognosis is dependent upon the seat and extent of the growth, as well as the importance of the organ or organs involved in the angiomatous process.

TREATMENT.—The aim and object of the surgeon in the treatment of all forms of angiomas is: to obliterate the vessels which constitute or nourish the growth, as by peripheral ligation or by compression; to destroy the growth with all its constituent elements by the interstitial action (necrogenic or vasculo-obliterative) of irritating, caustic, or other agents applied externally or introduced into the affected tissues; by the extirpation or excision of the angiomatous area in its totality. For

the accomplishment of these purposes a great number of methods have been recommended, some very valuable and practically useful, others very impractical and scarcely worthy of mention. In the selection of the method of treatment the surgeon must be guided largely by the special needs of the individual case, the nature of the growth, its situation, extent, depth, the organ or parts involved, complicating conditions (malignant associations, etc.). He should also be guided by the sex (in determining the effect of mutilating or disfiguring operations, on the face especially), the age, and general condition of the patient. In general terms, excision or extirpation is the *method of election* in all growths of limited extent which are well circumscribed and defined when they are situated in parts which can be sacrificed without involving disfigurement or the loss of important or vital organs. Sometimes extirpation—including amputation, in the extremities—is a *method of necessity*, the extent of involvement of the affected parts being so great that no conservative procedure is possible. Some of the methods recommended, such as ligation of afferent arteries, are only palliative, simply diminishing the growth of the tumors, and not radical; hence, the treatment may also be classified as radical and palliative. In a general way, the agencies employed to accomplish the objects of treatment, whether palliative or radical, may be grouped as follows:—

Compression Methods (direct mechanical compression with pads, adhesive plaster, acting by pressure in superficial nevi; collodion).—In very mild cases, and then only in very

young children, compression of the growth, or of the vessels leading to it, is recommended on account of its simplicity; but, as a rule, the effect is very slight and transitory after the infants are more than 3 months old. It is well proved that, in very young children, arterial angiomata and venous, as well as capillary, nevi are amenable to a cure by prolonged gradual compression.

Direct pressure with a disk of "sponge rubber," adapted to the size and contour of the growth or blemish, about $\frac{1}{2}$ inch thick, and held in place with a firm bandage, is the simplest, safest, and often the most efficient method of removing these blemishes in the newborn infant.

As advised by Stelwagon ("Diseases of the Skin," p. 645, 1903, second edition), the rubber pad is fastened to an elastic bandage—not the plain rubber bandage, but a loosely woven garter-like bandage, devised by G. H. Fox, of New York, and obtainable in the shops. The pad should be kept on constantly, only removing it to readjust it. This pressure plan is most successful in the first three months of infantile life, and should be given a fair trial whenever it is at all applicable. In other cases the pressure principle is more easily carried out by painting the surface 2 or 3 times daily with a mixture of 1 part of **ichthyol** to 9 parts of **collodion**. The nevus becomes compressed underneath the resulting pellicle until the rapidly growing surroundings have caught up with the excessive growth of the vascular tumor.

Superficial cauterization with caustics, sodium ethylate, fuming nitric acid, carbolic acid, zinc chloride, corrosive sublimate, caustic pastes (ar-

senic and zinc chloride, potassium hydroxide), the thermocautery and galvanocautery. Zinc chloride has been especially recommended for the purpose, as superior to all other methods of treatment, by Neumann, based upon practical experience with 700 cases, treated from 1900 to 1905. The remedy, in the form of a 5 or 10 per cent. sol. in flex. collodium, well shaken up, is painted on with a fine brush; it will in many cases prove sufficient to produce the mortification of the entire growth. Its action may be assisted by the addition of **arsenic** or **chromic acid**. In case of partial failure, the remnants of the growth should be covered with an **arsenic paste** (acidi arseniosi et sulph. depur., āā 4.0; ung. cerei, q. s. ad 100.0). This paste may be left in place for eight to twelve days, under aseptic dressings, the remnants of the growth becoming detached in the interval, leaving a smooth, slowly granulating wound surface. Or the necrotic portions may be removed at the end of the first forty-eight to seventy-two hours with a sharp curette. There is no danger of hemorrhage, provided the preliminary treatment has been of sufficient intensity. On account of its toxicity, the surface treated with arsenic paste should not be too extensive; it should be remembered that the action of arsenic is not only local, but progressive (gangrene). Although this contingency hardly enters into consideration in ordinary cases of telangiectasis and heman-gioma, the arsenic paste may be supplanted by parenchymatous or interstitial injections of dilute **zinc chloride**, which has no toxic effect. Surfaces measuring 30 to 40 sq.cm. and over may be destroyed at one

time without fear of absorption. The danger of infection is inconsiderable (none in 700 children treated by this method). Parenchymatous injections are especially applicable to those cases in which the emulsion treatment cannot be carried out, as, for instance, in the mucosa on the inner surface of the lip.

Series of 700 cases treated as follows during five years with favorable results by a bloodless method. The writer applies an emulsion of from 5 to 10 parts of **zinc chloride** in **collodion** to 100 parts. A piece of adhesive plaster is first placed over the angioma, with a hole corresponding to the lesion, but somewhat smaller, as the action of the chloride extends a little way under the edges of the plaster. This dressing is removed the next or on the second day, and the lesion cleansed and left to nature under a fresh, merely protecting dressing. The defect usually heals rapidly, sometimes in a week. If relics of the angioma still persist, he applies an **ointment** containing **arsenous acid** and **sulphur**, each 4 parts, with **unguentum cerei**, to 100 parts. The sound parts are protected with fenestrated gauze, and this paste is applied on another piece of gauze. In two or three days this dressing should be removed. Zinc chloride in the above dosage has no toxic action, and no absorption need be feared, even on an area of 30 or 40 square cm., but the arsenous acid is liable to cause toxic accidents. When possible, he substitutes parenchymatous injection of zinc chloride. Neumann (Deut. med. Woch., Bd. xxxi, Nu. 20, 1905).

Fiorani's method of removing nevi consists in the application of **corrosive sublimate** dissolved in flexible collodion. Several applications may be required, and a 13 per cent. solution is recommended. Dressings are unnecessary and the nevus may be al-

lowed to atrophy undisturbed after the desired caustic action has been produced.

Three cases of angiomata cured by Fiorani's applications of **collodion** containing 13 per cent. of **corrosive sublimate**. When the eschar dropped off, the parts beneath were found covered with normal epidermis, the angiomata having been completely destroyed by the caustic applications. Bindi (Gaz. degli Osped., vol. xxv, No. 145, 1905).

Cauterization with fuming nitric acid is a simple and efficient remedy in certain superficial nevi, producing a scab of sufficient depth, which becomes spontaneously detached and leaves a smooth, delicate cicatrix in its place. During the cauterization, the surrounding skin should be carefully protected with strips of adhesive plaster. This form of treatment is not adapted to nodular nevi or growths which are raised above the skin surface or distributed subcutaneously.

Ogata, a Japanese surgeon, recommends the following preparation as a local application for the removal of nevi and telangiectases. **Rice grains** are washed and placed in a glass dish; 10 per cent. **potassium hydrate** solution is poured over them, and they are allowed to stand six to eight hours after they have become thoroughly softened. The starch of the rice grains swells up and gradually becomes transparent. When the grain has become entirely clear the alkali solution is poured off and the sediment is washed with water. The mass so obtained is triturated in a porcelain mortar and forms a colorless, sticky mass, strongly alkaline in reaction, and consisting of a combination of starch with potassium hydrate.

Through the union with the starch the caustic properties of the alkali are considerably reduced and the tissues are not invaded too deeply. The preparation loses its strength in about six hours and therefore must be freshly prepared. It is applied by means of a pointed glass rod after the skin has been cleaned with tincture of soap and dried off. Several applications can be made at a single session, the area being washed with **sterile salt solution** each time after the caustic applied has dried. In children it is advisable to apply 5 per cent. cocaine solution before the caustic. In most cases 3 to 5 applications are sufficient, the area treated becoming black and being cast off in from seven to ten days. The scars are at first red, but later whiten and become entirely invisible. It is important not to treat too large an area at a time; otherwise, disfiguring scars due to suppuration may result. Lesions of considerable size require a treatment of months or even a year.

Freezing by the application of **liquid air** has been very successfully utilized in the treatment of superficial nevi and other growths by Trimble (Trimble, W. B.: *Med. Rec.*, New York, 1905, vol. lxviii, 58-60; *Inter. Dermat. Cong. Trans.*, New York, 1908, 1, 449), Dade, Whitehouse, and others.

On account of the practical difficulty in the way of readily obtaining and handling liquid air, the substitution of "**congealed carbon dioxide**" or "**carbonic acid snow**" as a more generally accessible and manageable agent has recently come into general practice in dermatological clinics in this country, since this mode of treatment was first introduced by Pusey, of

Chicago, 1908. Other dermatologists had previously reported on the value of refrigeration in the treatment of various dermal lesions. Arning, 1903, and Max Juliusberg (*Berlin. klin. Woch.*, 1905, No. 10) had tried **liquid CO₂** in the form of spray, for tissue destruction. The vast superiority of the "snow," however, as suggested by Pusey, marks a distinct advance in the technique, which has been fully confirmed in the treatment of nevi by Heidingsfeld, Waxham, the Ochsner brothers, Zeissler, A. Strauss, Hoffman, Sauerbruch, and others. The technique as usually carried out is as follows: From a cylinder of carbon dioxide such as is used in making frozen microsections, a fairly strong jet of the gas is played on to a piece of cotton-wool; the rapid evaporation of the cotton-wool causes intense chilling, which condenses a portion of the gas into a snowy powder with a temperature of 70° C. Some of the solidified gas is applied to the surface of the nevus, where it remains from ten to twenty seconds. The intense cold causes extreme contraction of the blood-vessels and anemia of the growth. This is repeated once or twice in the same sitting, the white flakes being applied to the different parts of the vascular surface. The snow may also be molded into suitable applicators. Pusey stamps it into an ear-speculum or into cylindrical hard-rubber tubes of different widths. With the former, one has a cone-shaped cylindrical mass which permits a freezing surface of variable size according to the lesion to be treated. The applicator is best handled through a piece of chamois skin or through a glove. The duration of the freezing should correspond

to the intensity of the effect desired. Superficial lesions can be destroyed in from five to ten seconds. Deep-seated growths, whose thorough destruction is contemplated, may be treated even for a whole minute. The physiological effects upon the frozen area vary, according to the time of exposure, from a simple erythema to necrosis. A bulla will form, as a rule, after five to ten seconds of deep freezing when the epidermis is intact. Raw surfaces respond with free serous exudation. "Notwithstanding very energetic freezing, the final result is, cosmetically speaking, eminently satisfactory and the resulting scar is perfectly smooth. It would be difficult to compare the method in this regard to any known form of destruction of tissue, as that of electrolysis, escharotics, caustics, or pure surgical means. This feature, as well as the comparative painlessness, the rapidity of the work, the avoidance of open wound and therefore of infection, makes CO₂ easily the most elegant and safest of all destructive agents (Zeisler).

Bibliography.—Pusey, W. A.: Berlin. klin. Woch., 1908, xlv, 1146-49; Heidingsfeld, M. L.: Lancet-Clinic, Cincin., 1908, xcix, 197; Waxham: Denver Med. Times, 1908-09, xxviii, 388-393; Zeisler, Jos.: Jour. Cut. Dis. and Syph., Jan., 1909, xxvii; Sauerbruch: Zentralbl. f. Chirurg., No. 1, 1909; Strauss, A.: Deutsch. med. Woch., 1908, xxx, 2312; Low, R. C.: Carbonic Acid Snow, W. Wood & Co., N. Y., 1911.

Pusey's treatment of angiomas and nevi with **carbon dioxide snow** used in 250 cases of angioma or nevus, with permanent cure in 93 cases. Nothing compares with the treatment, excepting perhaps radium, the X-rays, and the mercury quartz lamp. The dioxide treatment is simpler and less expensive than either of the above. It

destroys the skin and upper layers of the subcutaneous angiomatous tissue, leaving the epithelium intact. It is applicable to simple superficial angiomas, diffuse red pigmented nevi and brown nevi, and telangiectasia, but not to plexiform angiomas and cavernomas. Salomon (Deut. Zeit. f. Chir., May, 1911).

The face and flexor surfaces are most sensitive to the treatment. Women, particularly blondes, are more sensitive than men, while children are three or four times as sensitive as adults.

Immediately after the application of the **carbon-dioxide snow** the area treated appears white, depressed and hardened, and upon thawing, which requires one to three minutes, an erythema develops. Within two to twenty-four hours a vesicle forms upon the area treated, and this is replaced by a crust in two or three days. In nine to fourteen days the crust separates, leaving a smooth scar of normal color or of a slightly pinkish tinge, which becomes normal within a week or two. During the freezing process the patient experiences but little discomfort, but when the thawing begins a moderate amount of burning is usually felt and sometimes a transient neuralgia develops.

In freezing growths on or near the eyelids a piece of dry cotton should be placed between the lid and the eyeball to prevent the freezing of the latter tissue. The same precaution holds good when growths at the borders of the lips are frozen.

The number of treatments required varies with the severity and depth of the nevus, but in a large majority of cases one treatment will suffice. In the writer's series of cases cures have been accomplished in a large majority of instances, and improvement has been noted in all. Little after-treatment is required, the application of equal parts of zinc-oxide ointment and petrolatum being all that is necessary. G. H. Mize (Calif. State Jour. of Med., March, 1912).

In Bier's clinic the **carbon-dioxide** method of treating superficial simple angiomas and diffuse vascular birth marks, telangiectases and brown-pigmented nevi is the most efficacious. It is not, however, adapted to plexiform angiomas and true cavernomata. Salomon (Deut. Zeit. f. Chir., Bd. cix, Heft 5-6, 1911).

Penetrating, or interstitial, cauterization with the **electrothermic cautery; ignipuncture; steam or hot air.** While all caustics are inferior to the knife, complete excision may be contraindicated for a number of reasons (deep-seated angioma of the face involving the mucosa of the cheeks; penetrating cavernous tumors of the cranium; extreme youth of patient, etc.). In these cases puncture with the electrothermic cautery may be attempted, provided the growth is not in the face. Not only is the resulting scar very large and unsightly, but more or less considerable loss of tissue is apt to follow, especially around the nose. Moreover, there is always the danger of infection extending to the cerebral meninges from a deep-seated angioma of the face or cranial coverings when inflamed. For this reason aseptic dressings are required until the scab has become detached. As a rule, this form of treatment demands numerous repetitions, either because a part of the growth has been left behind or because there is prompt recurrence.

Cauterization with hot air is curative for angiomas and all other vascular growths of the skin, except in cases in which the neoplasm has invaded the mucous membrane, where the knife is preferable. But few sessions are necessary; there is absolutely no hemorrhage; the scar-tissue formed is scarcely visible in small areas. After a few applications the skin becomes mummified, the blood

being driven inwardly. E. Holländer (Berl. klin. Woch., April 23, 1900).

After **ignipuncture**, which is performed with a small needle and repeated at a number of points, a plainly visible and disfiguring scar is sure to remain. The needle should be heated to a dull-red heat, as puncturing with a needle heated to a white heat is likely to give rise to hemorrhage. After the surface has been rendered aseptic, the punctures are made a few lines apart and in a radiating circle, beginning at the periphery and gradually proceeding toward the center of the growth (Hollaender, Snegniereff, Pinkus).

Steam and hot air have been recommended as useful in the treatment of vascular tumors. In favor of this method it is claimed that the procedure is not only bloodless, but that the cicatrization is perfect and, in the milder cases, practically imperceptible. Vascular tumors in any portion of the body, including the cavities, are amenable to the method. The entire treatment can be carried out in one session. The objection is that a special apparatus is required and that the extent of the burn is not readily controlled.

Agents which act by coagulating the blood-contents, exciting aseptic interstitial inflammations, ultimately obliterating the vessels of the neoplasm.

Electrolysis, Electropuncture, Electrocataphoresis (Mercuric Cataphoresis).

—**Electrolysis**, especially employed by Kaarsberg in the treatment of vascular tumors, acts by producing coagulation through chemical changes in the blood and in the tissues. The action consists in the combination of a caustic effect at the two elec-

trodes, with dissociation of the water into its chemical constituents. An alkali is produced at the cathode and an acid at the anode; with simultaneous rise of gas bubbles at the two electrodes (oxygen at the anode; hydrogen at the cathode). The danger of pulmonary embolism is inconsiderable, since we are dealing chiefly with hydrogen, and in minute amounts. Electrolysis has a destructive action on vascular tumors through the molecular disintegration of the tissues, with hyperplasia of the connective tissue; while rapid coagulation of the residuary blood takes place. The treatment requires general anesthesia and a somewhat complicated electrical apparatus. Electrolytic treatment was employed with excellent results in over 80 cases by Heuking, who uses the bipolar method, inserting both platinum needles in the tumor. He advocates the method in cases where: 1, the angioma is situated on the face and where disfigurement may result from the formation of the scar or contraction of the skin; 2, the tumor is extensive, especially in cavernous angioma, where surgical treatment might induce severe hemorrhage; 3, when the patient objects to surgical interference.

Bibliography.—*Electrolysis*.—Redard, P.: De l'électrolyse dans le traitement des angiomes et particulièrement des angiomes de la région parotidienne, Presse méd., 1908, No. 19, mars 4, p. 145; Alcaire, G.: Traitement des angiomes par l'électrolyse, Gaz. méd. de Nantes, No. 15, 1907; Kaarsberg: Arch. f. klin. Chir., Bd. xlviii; Heuking: Electrolytic Treatment of Angioma, St. Petersburg med. Woch., vol. xxvii, 1902; Stelwagon: Treatise on Diseases of the Skin, Phila. and London, 1905; Hardaway: St. Louis Courier of Med., vol. xx, 1886. *Radiotherapy*.—For general information on the application and effects of X-rays on cutaneous lesions,

including vascular tumors, consult the American textbooks by Williams, of Boston (McMillan & Co.); Pusey and Caldwell, Chicago (Saunders); Arthur & Muir's Practical Manual, London (Rebman, 1909); Wetterer's handbuch der Röntgentherapie, nebst anhang die Radium-Therapie (Nemnick, Leipzig, 1908), and Vaudet's Technique precise de Radiothérapie et de Radioscopie (Leclerc, Paris, 1908); Cowen: X-rays: their Employment in Cancer and Other Diseases, London, 1904; Belot: Radiotherapy in Skin Disease, Paris, 1904; Freund: Grundriss der Ges. Radiotherapie, Berlin and Vienna, 1903; Jutassy: Fortschr. aus dem Geb. der Roentgen Strahlen, Bd. 2, 1898.

High-frequency treatment has been successfully employed in cases of telangiectasis, in applications of five to ten minutes' duration each (Bulkley, Pfähler). Margaret Sharpe recommends a vacuum electrode of her own designing: "It is exhausted to a much higher degree than those usually made for use with the high-frequency current. It gives a bright-green fluorescence, even in daylight, gives off no sparks or perceptible brush discharge, does not heat, and imparts no sensation whatever to the skin, which does not redden. It is held in contact with the skin, some pressure being used in the case of nevus."

Coagulating and irritating injections of chemical substances (ferric sesquichloride, Piazza's fluid, carbolic acid, zinc chloride, chloral hydrate), mentioned only to be condemned. Parenchymatous injections of ferric sesquichloride especially have been known to cause suppuration, a most serious complication when there exists a communication with the brain. Thrombi may become detached and may be carried to the brain and lungs with a fatal outcome.

Boiling-water Injections (Wyeth).

—Boiling water has been successfully injected in a number of cases of superficial capillary angioma, with very slight subsequent scarring. Wyeth has had a special syringe prepared into which boiling water is drawn directly, and if necessary can be heated afterward over an Argand burner. The instrument is handled with asbestos gloves. The method, according to him, is a homemade, simple, and entirely aseptic procedure, and commends itself for certain hitherto discouragingly intractable cases.

Wyeth's method of treatment of angiomata by **injections of boiling water**, about 30 to 60 minims (2 to 4 c.c.) at a time, had no failures in a series of 26 cases. In every instance the results have been gratifying. Most of the lesions were on the face and scalp. Four patients had angiomata on the tongue, ranging from the size of a filbert to that of an English walnut. One had the lesion on the left gluteal region as large as a cocoanut; another patient presented a fusiform angiomatous growth on the right middle finger between the second phalangeal articulation and the knuckle, which tumor caused great pain. F. Reder (Jour. Amer. Med. Assoc., Jan. 30, 1915).

Alcohol Injections (Schwalbe).—

The underlying principle of this method is the local inflammatory reaction of the tissues, followed by sclerosis of the connective tissue with compression and final obliteration of the blood-vessels. The injections (1 to 4 cm. of 70 to 80 per cent. alcohol) are administered at intervals of several days, beginning at the periphery of the growth and gradually proceeding toward the center. Caution is required as regards the management of those portions where the skin is thinned out, since these localities are extremely liable to necro-

sis, with inflammation and hemorrhage. It is claimed in favor of the method that alcohol injections leave no scars, and also that they produce very little pain, so that general anesthesia is superfluous. The simplicity of the procedure permits its employment without special preparation or complicated apparatus, all that is required being a Pravaz or large hypodermic syringe.

Injection of hydrogen peroxide (Mosetig-Moorhof), which acts chemically and mechanically. The introduction of hydrogen peroxide into cavernous tumors is followed by grave alterations of the blood, especially when considerable amounts are employed. The hydrogen peroxide is almost instantaneously broken up into oxygen and water by the blood, with marked evolution of foam, which is accompanied by the coagulation of the fibrin contained in the blood. When the contact is prolonged the hemoglobin leaves the red blood-corpuscles and becomes dissociated. The coagulant effect of the remedy is probably accounted for by these chemical processes. Dangerous and sometimes fatal gas embolism in the lungs may follow the introduction of large amounts of hydrogen peroxide into the circulation.

The **introduction of magnesium darts or rods (Payr's method)**. The indications for this form of treatment are based upon the accurate understanding of the pathologic-anatomic peculiarities of vascular tumors. The treatment does not involve the danger of thrombosis or embolism, and complications due to infection have not been observed. The growth becomes obliterated without any disturbance of the general health, and the cosmetic results are claimed to be excellent. The minute orifice through

which the magnesium is introduced later on becomes entirely invisible. The treatment offers the advantage of a very simple technique, permitting its performance under local anesthesia with little assistance and no loss of blood.

The Payr procedure is especially adapted to the treatment of vascular tumors of the subcutaneous cellular tissue. Very superficial cutaneous growths are less accessible and present far greater technical difficulties. Vascular tumors involving the mucous membranes are least suitable, on account of their delicate coverings as well as the constant friction and irritation of the parts (mucosa of lips and buccal cavity in general). This form of treatment finds its chief indications precisely in those cases where the cosmetic problem is most serious (simple and cavernous vascular tumors at the chin, cheeks, ears, the surroundings of the eye, at the forehead, and at the neck).

The method, which is partly chemical and partly mechanical in its action, consists in the introduction of rods or arrows of magnesium in all directions, by way of a small incision in the skin. Subcutaneous vascular tumors of the cavernous type are especially well adapted to the magnesium treatment. Extensive processes of coagulation take place after the magnesium has entered the large blood-spaces lined with endothelium, and these processes are readily transmitted to the vicinity through the communications of each individual blood-space. When the cavernous tumor has been treated with a sufficient amount of magnesium, the result is extensive thrombosis, terminating in complete obliteration through organization of the clot. An essential requirement of success is that the metal be distrib-

uted as uniformly as possible in every portion of the growth. The magnesium darts should be arranged, as they are thrust into the tissues, somewhat after the pattern of a fan, so that all the parts of the cavernous tumor are interspersed with the metal. Magnesium is decomposed in the tissues with considerable evolution of the hydrogen gas (1 gram of magnesium will yield 1 liter of hydrogen). Hence the possibility that mechanical disturbances, created by the evolution of the gas in the tumor, may enter as a factor in the results of Payr's treatment.

Physical agents which excite trophic and nutritive changes, leading to degenerative and atrophic process in the angiomatous area. Chief among these methods are the various light treatments: **sunlight, Finsen, X-rays, ultraviolet rays, and radium.** Attempts to cure with the light treatment have recently been made with some success in cases of superficial angioma. Finsen reported 10 cases of vascular nevi, with 1 complete cure and all the others more or less improved. Pfahler considers that in expert hands the results of radiotherapeutic treatment are at least equal to those obtained by other methods. While it is essential to obtain a reaction sufficient to produce desquamation, there is danger of acting too energetically and producing a cicatrix still more disfiguring than the original disease. The X-ray treatment must not be assumed to have a specific effect on these conditions. It acts by producing a certain degree of inflammatory reaction, which is manifested in the blood-vessels as a proliferative endarteritis, in the tissues.

The well-known degenerative and

obliterative effect of the X-rays upon the blood-vessels, which favors the atrophy of the tissues subjected to their influence, would suggest that this mode of treatment is particularly adapted to the cure of nevi.

The theory of the X-ray treatment of vascular nevus is based on the production of scar tissue of such a character as to strangulate the vascular lesions. The smaller the area of vascular dilatation, the better are the prospects of obtaining the desired result through the acute reaction set up in the growth. For this reason this form of treatment is not promising in very large angiomas. During the exposure, the normal parts must be protected with sheet lead and other precautions prescribed by a good Roentgen technique. Comparatively mild ray treatment promises well in cases where the vascularity of the growth is due rather to the existence of a great number of minute or capillary vessels than a few of large size. In all cases dermatitis should be excited, allowed to subside, and excited over and over again if necessary. Unless the reactionary dermatitis is of a very severe character, X-ray treatment is not likely to be successful in cases where the nevus consists of very much dilated blood-vessels. It is in the treatment of extensive superficial nevi that the X-rays promise most. Usually, after each attack of dermatitis, the nevus will be found to have diminished in size, owing to the development of fibrous tissue and the occlusion of the smaller blood-vessels. Irradiation with the X-rays was first attempted by Jutassy, who attributed the successful outcome to a contraction, thrombosis, and obliteration of the

vessels induced by the treatment. While more tedious than most other methods, the X-ray treatment of small nevi or moles has the great merit of painlessness, and the resulting scar is less unsightly than that following the use of the knife or the electrolytic needle.

Radium.—The marked success recently obtained with radium in the treatment of new growths and cutaneous disorders by the great improvement in the methods of its application brought about in the last two years, chiefly through the efforts of the French experts at the Radium Institute of Paris, justifies an attentive consideration of the special claims of this agent as a cure for nevi and other vascular tumors. The great drawback of radium as a remedy is, first, its great cost, which is still prohibitive to the vast majority of individual practitioners, and, second, the expertness and special training required for its successful application. These conditions will restrict the use of radium, even more so than X-rays, to institutional practice or to special laboratories in which small groups of trained specialists will alone be capable of utilizing this remarkable substance to the best advantage.

[Radium has never been isolated. It is obtained from pitchblende, a compound of uranium. What is spoken of as radium is the sulphate, a carbonate of the bromide of radium. Enormous quantities of pitchblende have to be worked in order to procure a few grams of the mixed chloride of radium and barium. To prepare a gram of the chloride 10,000 kg. of the mineral must be treated. At present the commercial value of radium is artificially very high; "if radium ever sank to such a degree of cheapness that it was worth its weight in mere gold, it would be exceedingly cheap" (Treves). It is impossible to appreciate the

therapeutic value and the possibilities of radium without a general knowledge of its remarkable and physical properties. This information can be readily obtained by consulting some of the general textbooks and references given in the subjoined bibliography. We will simply recall the fact that "radium gives off heat; that it is phosphorescent; that if it is dissolved in water it decomposes the same into its component parts, but that its main property is its radioactivity. Radioactivity means that the rays given off by radium have the power of penetrating solid and opaque substances; the power of affecting a photographic plate; the power of producing fluorescence, and the power of rendering air and other gas as a conductor of electricity. In addition, it gives off an emanation which has properties even more remarkable than those of the parent body itself. It is this emanation which gives radium the power of rendering any body it touches radioactive. There are three rays given off by radium, which are known as the Alpha, Beta, and Gamma rays. The Alpha rays may exist alone. For instance, polonium, a radioactive substance, discovered by Mme. Curie, contains only Alpha rays. Alpha and Beta rays are absolutely distinct and independent; they can exist the one without the other. But the Beta rays and the Gamma rays are inseparable; they are never found dissociated. The Alpha rays are supposed to give off the heat, and they burn. They are capable of producing a very troublesome ulcer of the skin. The penetrating power of these three kinds of rays is expressed as follows: Taking the penetration of the Alpha rays as 1, they are stopped by a sheet of mica. The Beta rays have a penetrating power of 100, and will pass through a centimeter of lead. The penetration of the Gamma rays, on the same basis, would be represented by 10,000, and will pass through one inch of steel. The Alpha, Beta, and Gamma rays have a very close resemblance to the rays which are met with in the vacuum tube used in the production of the X-rays. The strength of radium is estimated by taking uranium as a unit. Radium is then represented by a radioactivity of 2,000,000; a piece of "quarter strength" will, therefore, have a radioactivity of 500,000. The powdered radium when placed on a disk or plate is covered

with a varnish of special make (discovered by M. Danne), which is unaffected by boiling, by alcohol, or by the heat of a sterilizer. Applied in this way on a flat surface, a few milligrams will go a long way, as every milligram is available. Put the same quantity into a glass tube and the agent is almost useless. Radium can be mounted on "gum elastic," as in the uterine stems employed, or it can be spread on silk or cloth, or anything that can be varnished. In other words, a little radium spread over an even surface is much more powerful, and can be much more exactly used than a bead of it in a glass tube. The advances which have been made recently in radium therapy have been the result chiefly of the improved technique of application introduced by the French experts (Wickham, Degrais, and Dominici), in which, instead of the radium salt being applied in a glass tube or aluminum box, it is spread by means of a varnish on any flat surface. It is the sulphate of radium, either pure or diluted with sulphate of barium, which is fixed by the varnish, this salt being chosen in preference to the bromide of radium, as it is insoluble, while the bromide is readily soluble. Instead of the simple tubes, which, up to a recent time, have been supplied by the manufacturers for therapeutic purposes, radium is now furnished in the form of various applicators on flat and other shaped surfaces, based on the type of apparatus now used in the Radium Institute of Paris. Quoting Sir Frederick Treves: "Radium must be ordered by a definite prescription. For the individual case a plate of a certain diameter is ordered, and the proportion of Alpha, Beta, and Gamma rays required will be stated in the prescription. The Alpha rays may have to be cut off. How? By a certain thickness of aluminum, a very thin plate. Then comes the question of the distance, How close should the plate be held? The closer it is held, the more intense the effect, but the narrower the area of action. How long shall it be applied? Dr. Dominici has made special use of ultra Gamma rays, the most penetrating rays of all, and allows them to act for hours at a time. This limited action is secured by so screening the plates that what passes through the patient's body are only the ultra Gamma rays, those of the most intense velocity and the greatest penetrating power."—R. MATAS.]

A knowledge of the properties of the Alpha, Beta, and Gamma rays is not only essential to meet special indications, but to bring into operation the so-called "specific" or "selective" action of radium, as distinguished from its purely destructive action. This selective action is one of the astonishing things about radium, as illustrated by the manner in which it picks out vascular tissue for destruction. Under its influence, this tissue, as met with in the angiomas, vanishes. Wickham and Degrais, of the Paris Institute, state that radium has a specific effect upon: 1, cancer; 2, tuberous angiomas; 3, keloids; 4, chronic pruriginous skin affections, such as chronic eczema, neurodermatitis, and pruriginous lesions of any sort. In regard to nevus, Sir Frederick Treves's estimate of the value of radium, based on his observation at the Radium Institute of Paris, is worth quoting:—

"It may be said, and I think without hesitation, that radium will cure any form of nevus. It can cure the 'port-wine stain.' I would ask surgeons at the present day what measure they have available by which they can say as much? It can rid a patient of a pigmented mole, of a hairy mole, two troubles practically incurable if the size exceeds certain limits. In connection with nevus, let me take four illustrative cases. One is that of an infant with a nevus on the crown of the head the size of a gooseberry. There is no means of dealing with such a growth except by operation. It was cured by comparatively short applications of radium. Here is another case a little more striking: a girl with an angioma of the eyelid the size of a plum. This

had been subjected to four operations. Twice it had been excised; twice it had been treated with the actual cautery, but with no benefit. It was perfectly cured by radium without trouble or discomfort to the individual. Perhaps a more striking case is that of a young woman who had had a nevus occupying the whole of one side of the face. She had been subjected to numerous operations, but with only very imperfect success—I should almost say with no success. But under the influence of radium—and the treatment was, of course, long extended—she was cured. The last case is also remarkable. It was that of a child of 12 with a fibrous angioma situated in the substance of the arm, free from the skin, which was uncovered and sound. The mass was the size of a hen's egg. It was treated with radium from two sides (the 'crossed-fire' method of Wickham and Degrais), and was entirely dispersed in four weeks. It is, I am bound to confess, a little astonishing that a solid mass of such magnitude—not a mere subcutaneous growth—should have vanished so readily."

When "port-wine marks" are superficial and not raised above the surface, Wickham and Degrais use apparatus of feeble radioactivity, but of comparatively large surface. Gradual discoloration is obtained by the repetition of its application. They advise that the treatment should be especially applied to those forms that are deeply colored and infiltrated.

[The following case will give some idea of the technique adopted at the Paris Institute in treating larger angiomas: "A baby showed on the scalp a large angiomatous tumor raised 2 cm. above the surface. Two apparatus were selected, and each enveloped in aluminum, $\frac{1}{10}$ mm. in thickness; six

sheets of paper, and thin rubber ^{*}tissue. Thus covered, these apparatus allowed 20,000 units to pass, composed of nearly all the medium Beta rays, that is, rays of medium penetrating powers. The two appliances were placed on opposite sides of the tumor, and applied thus daily for ten days for twenty minutes each day. Three weeks later the tumor had diminished by a quarter, and the treatment was then begun again in the same way. The treatment was thus repeated three times with intervals of three weeks' rest; the cure was completed without any skin irritation at any time" (*Brit. Med. Jour.*, March 27, 1909, p. 798).—R. MATAS.]

It is evident from what has been stated and from the collective evidence of trustworthy observers that **radium** therapy as applied to dermal lesions and neoplasms, especially those of vascular origin, has, in consequence of the new French technique, entered into a new and promising phase of experience, which is well worthy of careful study and investigation.

The student of radium in its surgical applications will find it especially profitable to consult Dr. Robert Abbe's numerous publications on the subject, as the most authorized expression of opinion and experience on radium in America.

Bibliography.—Makower, W.: *The Radioactive Substances: their Properties and Behavior*, London, 1908; Radium: its Physical and Chemical Properties. (Special article.) *Brit. Med. Jour.*, February 6, 1909; Treves, Sir Frederick: *Radium in Surgery*, *Brit. Med. Jour.*, February 6, 1909; Thies: *Action of Radium Rays on Various Tissues and Organs*, *Mitteil. d. Med. u. Chir.*, Bd. xiv, May 12, 1904; Blaschke: *Erfahrung, mit Radium behandlung*, *Berlin. klin. Woch.*, No. 8, 1906; Wickham and Degrais: *Traitement des angiomes (tumeurs vasculaires et taches de vin) par le Radium*, Paris, 1908; Bureau, G.: *Traitement des angiomes et*

des épithéliomes cutanés par le Radium, *Gaz. méd. Nantes*, 1909, 2me s., t. 27, 21-29; Du Bois, C.: *Nævus vasculosus de la face traité par le Radium*, *Rev. de la Suisse Roman.*, Geneve, 1909, t. 29, 34-36; Massotti: *Nævi traités par le Radium*, *Bull. et Mém. Soc. Méd. d. Hôp. de Paris*, 1908, 3 s., t. 25, 163-166; F. de Courmelles: *Electrolyse et Radium dans le traitement des angiomes*, *Acad. de Méd., Paris, Séance 7-14, juin, 1909*; Abbe, R.: *Radium in Surgery*, *Jour. Amer. Med. Assoc.*, July 21, 1906. Also Abbe, in "Jerome" Cochran lecture, *Trans. Alabama State Med. Assoc.*, 1908; Abbe: *Radium's Contribution to Surgery*, *Trans. Surg. Section, Amer. Med. Assoc.*, 1910.

Surgical Methods.—The most rapid and efficient means of dealing with vascular neoplasms are operative, and may be subdivided into:—

Peripheral, subcutaneous (buried) strangulating ligatures for circumscribed angiomata (Krogius), or the zigzag method (Beck). The application of a continuous series of subcutaneous ligatures in the entire periphery of the tumor is recommended by Krogius in the treatment of plexiform angioma. He proceeds as follows: "Two needles with a handle and flexible point (Lanblin) were employed, one slightly curved and the other more so. The strongly curved needle is introduced first, passing through the skin to the bone, and for a certain distance along the latter, finally coming out again through the skin. The needle is pulled out after it has been armed with a strong catgut thread. Through the same entrance orifice the other (slightly curved) needle is then passed out by the exit orifice immediately beneath the skin; one end of the catgut is threaded in, and the needle is then pulled out. The two ends of the thread are thus made to come out through the same orifice, where they are tied. The

hemorrhage from the stitched channels usually subsides very promptly after the thread has been tied, though it may be very readily controlled by compression. The next ligature is best applied in such a way as to overlap the exit orifice of the former ligature, the ligatures thus acting as chain ligatures without actually interlocking. An uninterrupted series of these ligatures is now placed around *the entire periphery* of the angioma, so as to strangulate, if possible, all the abnormally dilated vessels, thus inducing the shrinkage of the tumor. In case the first operation is not entirely successful, a second and smaller ring of ligatures may be applied around the persistent part of the angioma at a later session. If necessary, the procedure may be kept up until the last trace of the tumor has disappeared. It is of the greatest importance for the success of the treatment that no gap of any size should be left in the series of ligatures. In the originator's experience, these ligatures induce the obliteration of the dilated vessels with subsequent disappearance of the plexiform angioma, without interfering with the vitality of the skin.

A similar method for the treatment of ordinary angiomata was suggested by Karl Beck (Chicago), based on the principle of gradual transformation of the vessel masses into connective tissue. This is accomplished by subcutaneous suture as follows: "A thread of catgut is passed in a zigzag manner first below the skin, then underneath the base of the tumor, then again underneath the skin, underneath the tumor, etc., until the tumor mass is included in this continuous suture. The latter is drawn tight and closed at the point of entrance of the needle. In this manner the circulation is shut off within the tumor,

but no gangrene follows, inasmuch as some blood can yet reach the parts not included in the suture. The mass soon grows smaller and the normal epidermis outside of these limits stretches considerably, but becomes elastic and grows again. This procedure is repeated until the tumor is diminished to the smallest nodule of connective tissue. The hard connective-tissue masses are then excised and the edges carefully united. This treatment applies to all varieties of angioma, but in the arterial and mixed varieties it is necessary to ligate the largest afferent vessels in order to check the rapid growth."

Ligation of Large Afferent Trunks (for Cirroid or Other Local Afferent Vessels).—The ligation of the individual blood-vessels has been practically abandoned in the treatment of cirroid aneurism. The method is tedious and uncertain, and gives rise to more disfigurement than an excision scar. It has been successfully employed in cases of venous nevi where excision was impossible. The treatment may be supplemented by the use of strangulating buried ligatures, or injections of alcohol, etc., and firm bandaging, but it is unlikely that these will cure any cavernous tissue persisting after ligation of the main trunk.

Extirpation or Excision of the Tumor.—The ideal treatment of angioma is excision. Usually the extirpation of angiomata can be accomplished with comparatively slight loss of blood by attacking them from the periphery within the line of healthy tissue. It should be remembered, as Ribbert has demonstrated, that the angiomata are developed at the expense of an independent germinal bud and remain isolated to a large extent from the surrounding vessels, the diseased tissue

being usually defined by a more or less well-formed capsule. However, the safest course is always to prepare for serious hemorrhage and to make use of every available method of prophylactic hemostasis, including the provisional occlusion of the main afferent artery of the region. The author has found that the preliminary infiltration of the angioma itself and perivascular areas with **physiologic salt solution** containing $\frac{1}{10}$ of 1 per cent. of **B-eucaine** or $\frac{1}{3}$ of 1 per cent. **novocaine** and 10 to 20 minims of **adrenalin solution** (1:1000) to the total estimated amount of fluid required to densely edematize the field of operation will be found most useful not only as a hemostatic, but as an anesthetic procedure. The infiltration is obtained by forcing the solution into the tissues under considerable pneumatic pressure by means of the author's special apparatus (see illustration). The solution should be allowed to remain at least ten to fifteen minutes before operating in order to give time for the adrenalin to act in constricting the blood-vessels. The author has always applied this method in late years as a preliminary to the operative treatment of all accessible and well-defined angiomata.

The incision should be made a few lines away from the visible boundaries of the tumor, on the sides as well as its base. A skillful operator will sometimes succeed in removing the growth so quickly that no ligatures will be required until after the extirpation has been completed. Skin-grafting may be required for the covering of the raw surface. In favorable cases (distinctly outlined cavernous angiomata) extirpation of the tumor results in a linear or relatively invisible scar. Complete ex-

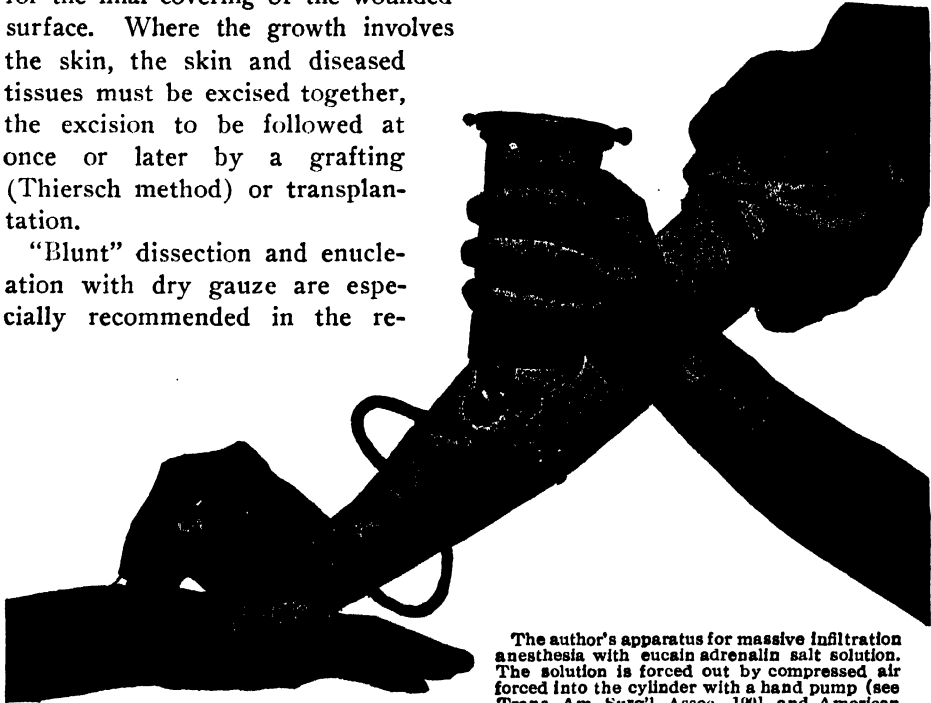
cision is adapted to the superficial as well as the deep-seated and encapsulated forms. When the growth is deep and there is no capsule it may be rapidly extirpated by means of the sharp curette (v. Bergmann), without fear of hemorrhage, since, after the removal of the large blood-spaces, the bleeding remains limited to a few afferent arteries. At the extremities bloodless excision is performed under Esmarch's ischemia, and at other portions of the body with the aid of digital or instrumental compression. A secondary plastic operation may be required for the treatment of remaining tissue defects.

Extirpation is also, according to present experience and statistics, the most important and efficient treatment of plexiform angiomata. The excision of a voluminous plexiform angioma of the head may be aided by previous ligation of the external carotid artery or by temporary compression with soft clamps on the common trunk. The application of a rubber tube around the head, as well as hard-rubber plates pressed to the skull in the temporal fossæ, have been found valuable. Cushing's elastic cranial constrictor is well adapted to this purpose. Circumligation of the tumor, followed in a few days by its extirpation, is justifiable in the aseptic conditions of modern surgery. Daily change of the occlusive bandage is required during the first three or four days following the operation. In the cases where the great extent of the growth precludes the use of the knife, some prospect of improvement is afforded by alcoholic injections. In tumors of moderate size and readily accessible on all sides, excision offers the best outlook. A large plexiform

angioma requires the preliminary ligation of several of the larger vessels. The incision must be made in healthy tissue some distance away from the growth. After the chief nutrient vessels have been exposed, they are caught with hemostatic forceps and divided. Healthy skin is reflected and preserved for the final covering of the wounded surface. Where the growth involves the skin, the skin and diseased tissues must be excised together, the excision to be followed at once or later by a grafting (Thiersch method) or transplantation.

"Blunt" dissection and enucleation with dry gauze are especially recommended in the re-

over the convexity of the tumor, if the superficial part of the skin is relatively healthy and participates but slightly in the formation of new vessels. A marginal incision is made where there is extensive vascularization of the skin. The periphery of the tumor is exposed under compression, followed by pene-



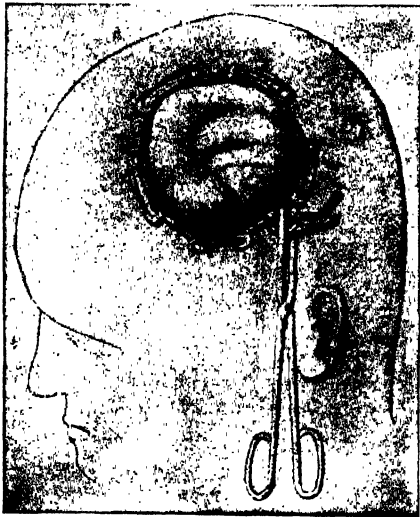
The author's apparatus for massive infiltration anesthesia with eucain adrenalin salt solution. The solution is forced out by compressed air forced into the cylinder with a hand pump (see Trans. Am. Surg'l. Assoc., 1901, and American Medicine, Phila., Dec. 28, 1901).

moval of certain cases of well-defined subcutaneous angiomata. The method is especially adapted to cases of large cavernous angiomata, simple angioma after it has assumed tumor proportions, and cases of mixed angioma in which all three varieties of vessels are represented. Even in enormous tumors in which other excision methods are inadmissible as too dangerous, the systematic and careful blunt and "dry sponge" dissection of all the prolongations of the growth may yield favorable results. An incision is made

tration of the deeper portions. Bleeding arteries or veins are caught up and tied. Not a single ligature may be required when the border of the capsule of the angioma is closely adhered to, so as to operate in healthy tissue. Dry "gauze" dissection is not so well adapted to the treatment of plexiform angioma.

Körte's method of extirpation (especially for plexiform angioma). Control of the hemorrhage is the main difficulty encountered during extirpation, and various methods

have been devised to diminish the amount of bleeding. These are discussed in detail by W. Körte (Deutsch. med. Woch. for August 29, 1907). He found that an elastic head bandage was of little avail in most cases, while previous ligation of the main trunk which supplies the tumor greatly diminishes the bleeding; if it is an angioma of the head the external carotid is tied. Of course,



Elastic constriction of the surface with the aid of transfixion ("safety") pins, applicable in the removal of large vascular tumors. (Senn.)

this does not empty the tumor entirely, as a collateral circulation sets in, and as some of its content is supplied through the skull. In addition, he passes a mattress suture through the skin around the entire tumor, about 2 cm. from its base; the growth is then extirpated within this suture, when the latter is removed and the bleeding vessels are ligated, the defect being closed by bringing the edges of the wound together. If the growth is very large, the skin edges cannot be brought together and the skin over the tumor must be pre-

served. After ligating the main trunk as before, the mattress suture is not passed all around the tumor, but in horseshoe-shaped fashion, and digital compression is made at the point (pedicle of the future skin-flap) where the mattress suture has been omitted. An incision is then made down to the periosteum just inside the suture line, when skin and tumor are rapidly dissected up together, the bleeding from the bone being easily controlled by gauze and pressure. The angioma can then be slowly dissected from the skin with practically no bleeding, while, if the skin were first dissected from the tumor before the latter was raised from the periosteum, the bleeding would be more profuse. The mattress suture is then removed and the vessels tied as before, and the skin-flap is sutured in place. Körte usually also extirpates the afferent vessels as well, but thinks the procedure unnecessary, as they get smaller spontaneously after removal of the main tumor. Extensive racemose angioma on the extremities offers greater difficulties, as the tying of the large number of vessels which require this may give rise to gangrene, so that amputation must be considered in the treatment of such tumors.

A new procedure for the obliteration of superficial vascular nevus was devised by L. L. McArthur, consisting in a section of the integument on a plane horizontal to the affected surface, in such a way that the entire thickness of the integument is not destroyed, but that the knife passes through each capillary loop as it comes to the surface. The idea is to preserve sufficient intact integument to prevent its actual perforation with protection of the con-

nective tissue beneath. Application of thin Thiersch grafts after the blood in the undivided capillaries has coagulated results in obliteration of the divided capillaries through plugging with blood-clot, and the graft, becoming organized, conceals the pigmented appearance of the blood-mark. The method was successfully adopted in a case which had already been treated by electrolysis and various other procedures for the destruction of the vessels had been applied without benefit.

Amputation.—There are certain extreme conditions which in spite of all treatment remain a constant source of danger on account of progressive growth, pressure on the surroundings, hemorrhage, and suppuration. Under these circumstances any form of treatment which does not completely and radically destroy the growth only aggravates the condition by stimulating the vessels to increased proliferation and extension. The sacrifice of the affected extremity by amputation becomes then a matter of necessity.

The foregoing methods of treatment may be summarized as follows: On all newborn babies with well-defined "mother's marks" or limited angiomata, first try direct **mechanical compression** by Stelwagon and Fox's method; then **collodium** and **ichthyol** as a second choice. If this fails, as it may, in older infants, try, according to circumstances and available resources, applications with **liquid air** or **carbon-dioxide "snow,"** by the Pusey method. If **radium** is available, its application by the new French technique should be preferred over other methods, in the hands of a thoroughly competent expert, as the most satisfactory treatment, especially for the more extensive, deep-colored "port-wine" spots, and

the larger or tuberous angiomata. This is particularly true when the nevi occupy conspicuous places and invade the vicinity of important organs (eyes, nose, ears). When radium is not available, the **X-rays** and **electrolysis** are worthy of trial. In the more superficial and deep-colored nevi, **superficial cauterization** obtained with application of a **zinc chloride emulsion** (Newman) or a **bichloride collodium paint** (Fiorani) or even **Ogata's Japanese caustic** is well worthy of trial. Whenever a well-defined circumscribed and elevated angioma can be surgically removed without disfigurement, deformity, or danger to life, it is best—after a fair trial of the bloodless methods previously mentioned—to **excise** the angiomatous mass after a previous massive anesthesia and ischemia with a B-eucaine (or novocaine) adrenalin saline solution injected by the author's method.

When the usual methods of prophylactic hemostasis are unavailable, and it is evident that a surgical extirpation would be hazardous on account of hemorrhage or involvement of important organs, the bloodless methods of tissue strangulation by the **buried ligatures** of Krogus, Beck, and others should be considered. In some cases a combination of methods may accomplish the best results, the strangulation of the tumor by ligatures being preceded or followed by a course of interstitial sclerogenic injections induced by **alcohol** or **Payr's magnesium darts**. It is in the large cirroid aneurisms of the head and scalp, which involve widely diffused arteriovenous plexuses, that the resources and ingenuity of the surgeon are the most seriously taxed. It is only in the extreme, almost monstrous, types of this disease (plexi-

form angioma) that nothing but a merely palliative course can be pursued. Fortunately these extreme cases are likely to become still less frequent in practice as the advantages of early treatment and the superior forces now at the command of the modern surgeon become better known and fully appreciated.

Whenever ulceration and hemorrhage threaten life, provisional hemostasis may be obtained by direct **mechanical compression** over the bleeding point, the pressure being applied over a non-irritating antiseptic hemostatic powder held in a sterile bag or sachet, which will form a firm scab and remain in place until granulations have developed (**ferripyrrine, Squibb's compound alum powder**, etc.); or the bleeding may be promptly arrested by suturing the bleeding area percutaneously pending more definite and radical measures. The ligation of the main artery of the region involved is, as a rule, only a palliative measure which is rarely of value except as a provisional hemostatic or denutrient, to starve rapidly growing tumors.

The injection of **quinine and urea hydrochloride** has been resorted to with success by W. Wayne Babcock (N. Y. Med. Jour., Mar. 3, 1917) for the destruction of angiomas and other new growths. He found it to offer the advantage, as a necrotizing substance, of being more readily handled than boiling water, and of not coagulating blood nor producing serious toxic symptoms should it enter into the blood-stream.

While the injection of the solution causes intense though transient pain, marked secondary edema, a sluggish ulcer, a transient induration of the scar, and the possibility of serious symptoms from a quinine idiosyncrasy, the advantages of the method are: the intensity of the necrosis produced even in very vascular tissue; a secondary persistent anes-

thesia; the low toxicity of the substance employed; the convenience of the application especially upon mucous surfaces or other regions of the body that are not readily accessible.

In angioma of the inside of the cheek injection was followed by the escape of a few drops of blood from the needle puncture, after which there was rapid necrosis, the slough separating without any evidence of hemorrhage and with complete removal of the tumor. A painless edema involving the entire half of the face largely subsided at the end of a week.

Babcock has tried the method also in internal hemorrhoids (using a 12 to 60 per cent. solution), urethral caruncles, warts, moles, keratoses and superficial and deep epitheliomas. He suggests that the injection of quinine and urea hydrochloride about a malignant growth may, by the production of edema, lymph blockage, and fibrosis with intense necrosis in the area of the injection, constitute a valuable agent in the removal of the tumor and in the prevention of metastasis, though he observed recurrence in 1 epithelioma of the face after 2 injections. In carcinoma of the pharynx and tonsil the method should be tried, also for post-pharyngeal fibromas. Introduced into the enlarged faucial and lingual tonsils, the injection is practically painless, much of the solution escapes, and the secondary necrosis is insufficient.

The technique followed by the writer is as follows: An ordinary hypodermic syringe is employed, and for convenience, a 33 per cent. and a 50 per cent. solution of quinine and urea hydrochloride is prepared in ampoules containing 2 c.c. (32 minims) each. With a fine needle the affected area is infiltrated, taking care not to infiltrate too widely. The chief action of the injection is to block the circulation and cause ischemia; therefore the entire area is infiltrated, or a proximal infiltration is so given as to cut off the blood-supply. In treating sensitive areas the preliminary injection of a $\frac{1}{2}$ to 1 per cent. **novocaine solution** may be desirable to prevent the initial pain.

RUDOLPH MATAS,
New Orleans.

BLUE MASS. See MERCURY.

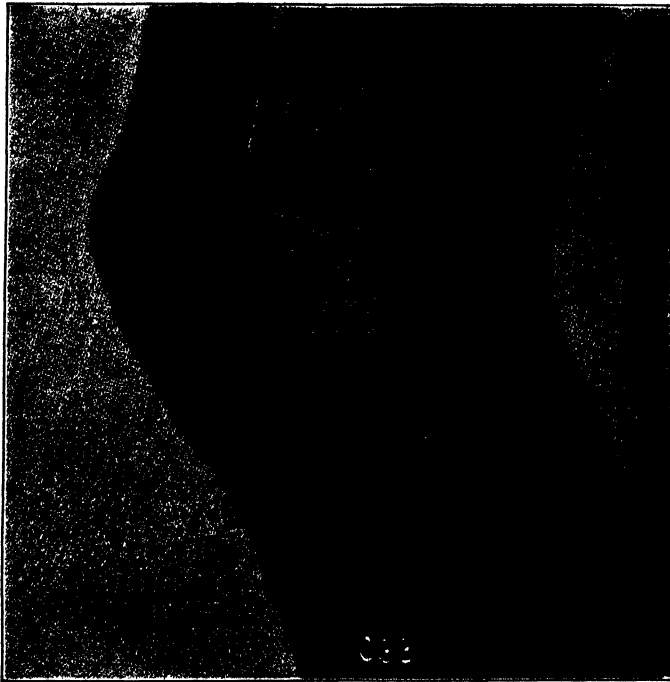
BOAS-EWALD TEST-BREAK-FAST. See ACIDITY OF THE GASTRIC CONTENTS, TESTS FOR.

BONES, DISEASES OF.

PERIOSTITIS.—Inflammation of the periosteum.

SYMPTOMS.—When an ordinary acute periostitis follows an injury

liable to be mistaken for pus, but the surface is usually not so red as when pus is present. The anterior surface of the tibia, being most exposed, is the most frequent site of the trouble, but the clavicle and other bones may also be affected. When no infection occurs from purulent micro-organisms, suppuration may not occur. If, however, the acute form



Roentgenogram of traumatic periostitis. (*Dieffenbach.*)
(American Physician.)

there is a localized swelling, redness, heat, and pain—which is usually worse at night. The tenderness is exquisite and the use of the part is much interfered with. A spindle-shaped enlargement can often be felt, due to thickening of and effusion into the periosteum, with sometimes detachment of it from the underlying bone. A collection of blood may form between the detached periosteum and the bone beneath. This collection is

supervenes during some infectious disease, suppuration is apt to take place, and constitutional symptoms—severe in proportion to the extent of the inflammation—ensue. Even should the involved area not be extensive, suppuration is apt to be prolonged and extremely obstinate, in some cases causing death from exhaustion. Diffuse periostitis is a serious variety in which the inflammation spreads rapidly, sometimes in-

cluding the periosteum of the entire shaft. It may reach the epiphyses and the joints and extend deeply into the osseous tissues, perhaps as far as the medulla. Pyemia sometimes appears in these cases and generally ends fatally, although in children recovery may ensue even after meta-

a complication in the young than in the adult and may make its appearance long after all symptoms of the original infective disease have subsided and the patient is apparently well.

It may be primary, or secondary as the result of inflammation of the



Roentgenogram of periostitis following typhoid fever. (Dieffenbach.)
(American Physician.)

static abscesses have shown themselves in several parts of the body.

Periostitis frequently follows injuries; it may also arise spontaneously as a sequela to variola, typhoid fever, scarlet fever, and other infectious diseases. The complication, as a rule, however, only occurs at the end of convalescence. After typhoid fever the tibia is usually implicated, and the jaws after scarlatina and measles. Periostitis more frequently occurs as

underlying bone or the medulla. In syphilitic and tuberculous subjects a local periostitis may arise without any discoverable traumatic cause. It is probable, however, that in many of these apparently idiopathic cases there has been a previous unnoticed trauma, but of a degree which would not have affected a healthy periosteum.

Three cases of chronic non-suppurative osteoplastic periostitis due to a single severe crushing injury. In

all 3 cases the original injury to the thigh was severe, and temporarily disabled the victim. In all cases prompt and almost complete recovery from the concussion followed. Only after some weeks or months did there occur local symptoms to indicate that anything more serious than a bad bruise had resulted from the impact. Pain began to be noticed in the affected thigh. It was worse at night and of a dull, boring character. A local tenderness appeared. Walking began to produce discomfort and there was associated a limping gait. The general health in all patients became impaired. In all cases after removal of the first growth there was complete relief of pain, and each man began to gain in weight and the pallor disappeared. Pickrell and Schmidt (U. S. Naval Med. Bull., Jan., 1910).

Correctly managed, we can almost create bone at will from the periosteum. The balance and co-ordination between bone and periosteum are like those between the derma and the epidermis. Repair of bone requires always the co-operation of bone tissue and of the neighboring soft parts: It depends on the periosteum physiologically understood. There is no specific bone-producing layer between the bone and the fibrous stratum, and bone is not secreted, in the strict sense of the term. It forms by the junction of bone and the fibrous tissue, represented by the periosteum, the outer layer of the bone participating, as they show by microscopic views of newly proliferated bone. The new bone grows out like a tumor in the direction of least resistance, but there can be no bone growth from the periosteum unless the superficial layers of bone have been scraped off with the periosteum. Leriche and Policard (*Presse méd.*, Mar. 18, 1918).

PATHOLOGY.—The morbid changes consist in a temporary thickening of the periosteum, followed by rapid cell-proliferation and the formation of inflammatory lymph. When

pus forms on bones which are subcutaneous, as the tibia or clavicle, if the process is acute, the skin and overlying soft parts may soon be perforated and a discharging sinus is formed. The parts may remain thickened or hardened (sclerosed), though the underlying bone, through defective nutrition, becomes soft. Especially in chronic processes healing may occur without external suppuration, and then the surface remains rough and uneven, due to the bony deposit from the diseased periosteum. Diffuse inflammation so reduces the osseous nutrition sometimes as to cause death of bony areas: caries, necrosis (see *OSTEOMYELITIS*, farther on in the present article).

TREATMENT.—Many cases of periostitis are kept active by the continued irritation of the part through lack of rest. It is strange that this fact is not more generally recognized and appreciated. All sorts of ointments and medicaments are often applied, yet the most important element of treatment—**rest**—is neglected. The muscles being inserted in the periosteum, their contraction disturbs the latter, and the periostitis cannot subside. The first indication, therefore, is to order the patient off his feet if the lower extremity is involved or thoroughly immobilize the part if in the upper extremity. Not only should this be done, but all movements of the affected member should be prevented by encasing the limb in a **plaster-of-Paris dressing** or securely bandaging it to a **splint**. Not only should the part immediately involved be splinted, but also the regions, especially the joints, above and below, so as to prevent the adjacent muscles from disturbing it. The foot should

always be kept at rest and preferably elevated when the lower extremity is involved, and the hand when the upper extremity is affected.

Local depletion is also efficient. **Leeches** may be applied or multiple **punctures** of the swelling may be made with a slender tenotome or cataract knife. Instead of these punctures, a **subcutaneous incision** may be made through the swollen tissues down to the bone. We have seen such an incision give almost immediate relief in a periostitis affecting the femur which had been causing pain and total disability for several weeks. This puncture or incision should be done with proper antiseptic precautions. In chronic, troublesome cases in which the upper layers of bone are involved, making an **incision** down to the bone and then **boring** several small holes into it—the aim being to **relieve tension**—and finally putting the limb in **plaster of Paris** has been followed by the most gratifying results in my hands. To wait for the formation of pus in these cases before operating is, in the highest degree, undesirable, as an earlier boring of the bone cuts short the disease at once and prevents the occurrence of suppuration. In those cases of acute infection involving areas of considerable extent and accompanied with high fever and other evidences of constitutional sepsis, free incisions down to the bone splitting the periosteum wide open under anesthesia are to be made at once.

OSTEITIS.

Inflammation of the osseous tissue proper is seldom, if ever, witnessed as a primary affection and without involvement of the medulla. The osseous structure is often involved,

however, in periosteal and myelitic disorders. The symptoms are described under *periostitis*, but they are somewhat more marked as regards pain and tenderness, while greater ambulatory impotence exists. When tuberculous infection is the underlying cause the onset and course of the disease is frequently insidious and slow. Marked pain and constitutional disturbance may only become manifest when the surrounding parts have become extensively involved.

ETIOLOGY AND PATHOLOGY.

—After a bone injury, as in the case of fracture, blood and serum are effused at the affected spot. The periosteum and surrounding parts become infiltrated with leucocytes. From the periosteum and the adjacent bone stellate cells are proliferated. The effusion in which they occur becomes first hardened and striated and lime-salts are deposited. The stellate cells become full-fledged osteoblasts, which finally develop into bony tissue. In cases resulting from simple injury the natural state of affairs is soon re-established, but occasionally an anomalous course is pursued. The bone may become uniformly increased in all dimensions, constituting a true **HYPEROSTOSIS**, or, if the density is increased as well as thickness, an **OSTEOSCLEROSIS**.

The writer draws attention to the seriousness of the fistulous complications which follow bone injuries in war. Surgical treatment alone is capable of promising recovery to the patient.

In investigating the signs and conditions of an osteitis he gives particular emphasis to the value of radiography. Every patient with a wound which will not cicatrize ought to be examined radiographically at once. Aside from those cases in which the

suppuration is due to a retained projectile, when there is an osteitic area radiography will show the modifications in the volume of bones as well as the structure of new bone, which shows quite differently from normal bone. In a fracture area radiography will show rarifying and condensed osteitis, osteitic cavities, subperiosteal callus, etc. The author thinks that radioscopy in such cases is useless. It is by radiography alone that the lesion must be read. Haller (*Presse méd.*, 581, 1917).

In this disorder the bones of the head are most often affected, and the disease may last many years.

When osteitis attacks the bones of the face a very peculiar appearance results, to which Virchow has given the name *LEONTIASIS OSSIIUM*. The disease begins in youth in otherwise apparently healthy persons and lasts many years.

Posttraumatic osteitis of the carpal scaphoid bone is not very rare, the writer having seen 6 cases. As a rule, the condition pursues the following course: After a fall upon the hand there develops, with swelling and pain, usually a slight limitation of motion, and tenderness over the scaphoid, especially in the *tabatière anatomique*. The Röntgen rays showed in 5 cases a more or less round or elongated clear space, which often involved the whole of the scaphoid. A primary fracture does not seem to precede it. Gradually the defect increases, the walls break through, and the scaphoid finally gives about the same picture as a recent fracture. The clinical course is very chronic, the disturbances remaining only in mild degree. The condition probably originates in a primary tearing of the dorsal ligament between the scaphoid and semilunar bones, which leads to a disturbance of the nutrition of the central portion of the scaphoid, with resulting rarefying osteitis, which shows in the skiagram as a visible

defect and finally causes a spontaneous fracture. Preiser (*Zentralbl. f. Chir.*, Bd. xxxvii, S. 929, 1910).

TREATMENT.—This does not differ from the treatment of inflammation in the soft tissues. Prompt and radical surgical measures may localize the morbid process, but if it is quiescent it need not be disturbed until a sequestrum becomes detached with the cavity. Then the latter may be freely opened, the sequestrum removed along with what granulations are present, and the cavity swabbed with **carbolic acid**. Removal of the infected material is usually followed by healing and the reproduction of bone.

The writer has compared the results in acute purulent osteitis of the fibula treated by various methods. Seven cases are reported in detail as typical of the various experiences. In the cases in which treatment was by subperiosteal resection of the shaft, the lesion healed promptly and permanently, while with the more conservative measures the affection dragged on tediously or recurred again and again. This resection of the shaft does not interfere with normal growth or functioning, while the prompt removal of the focus removes all danger of sepsis. Sulzer (*Münch. med. Woch.*, July 11, 1911).

A study of 60 cases led to the following conclusions:—

1. The mortality and extent of the necrosis following acute inflammation of the bone depends not only upon the promptness of surgical interference, but also upon its thoroughness.
2. Suppuration beneath the periosteum does not exclude an infection of the medulla, the presumption being that after three days the medullary cavity is also involved.
3. Within seventy-two hours of the onset of the disease osteoperiostitis is localized, usually in the cortex of the bone, and incision, disinfection, and drainage are sufficient to bring

about a cure. If there is no marked diminution of the symptoms in twenty-four hours after incision and drainage, the medullary cavity should be opened. 4. When the medullary cavity is opened and found healthy, the dangers of infecting it are slight. 5. In the majority of cases osteomyelitis is due to a neglected osteoperiostitis. 6. In operations after the third day, where systemic symptoms are pronounced, the medullary cavity should be always opened, and the opening should be sufficiently long to expose healthy marrow, and sufficiently broad and long to expose healthy bone. 7. The mortality of 10 per cent. was directly due to delay in operation and conservatism at the primary operation. In 5 of these cases, had a radical operation been performed recovery probably would have been the result. Le Conte (Boston Med. and Surg. Jour., June 1, 1911).

Nine patients with chronic osteitis of the mastoid or temporal region consecutive to middle ear disease were cured under **carbon arc light** exposures. The treatment occupied up to 9 months in some. The benefit was equally pronounced in the tuberculous and the apparently non-tuberculous cases running a protracted course. O. Strandberg (Hospitalltidende, May 1, 1918).

The introduction of **bismuth paste** into the sinus advocated by Beck, of Chicago (see article on Bismuth, this volume), has given good results, though the use of this measure requires care to prevent poisoning. Injections of **iodoform** and **spermaceti wax** after a preliminary curettage were also advocated in certain cases, especially tuberculous, and when the bone would not be too much weakened by the treatment removal of all the diseased tissues, allowing the soft parts to fall in over the deficiency, has also been advocated.

Where a deep recess in a bone has been left through removal of bone tissue for osteitis, the writer makes superior and inferior transverse skin incisions above and below the site of disease. The resulting lateral flaps are mobilized for some distance and then drawn together down into the center of the bone defect. Three to 6 radiating incisions may be made to permit better coaptation of the skin flaps over the defect. Dressings being insufficient to hold the flaps in place, the author, after retracting the flaps laterally, makes holes with an awl through the bone and passes through them bronze wire, which issues near the bottom of the groove in the bone and holds the margins of the flaps down in place. Usually 2 or 3 bronze sutures are used for each flap. At both ends of each bronze wire a small packet of gauze is placed to prevent injury to the skin. After having been fastened with the wire, the flaps are united at their margins by a few sutures. The bronze sutures are kept under observation on and after the third day, and are removed whenever the pressure at the point of fixation is seen to be threatening the vitality of the flap. A number of cases of osteitis after war wounds were treated successfully by this procedure. D. Thevenard (Presse méd., Oct. 7, 1918).

A bone should never be resected for a single focus of fibrous osteitis. In a case in a girl of 10, roentgenograms showed bone tissue gradually filling up the cavity of the solitary cyst after curetting. Eleven months later not a trace of the cavity remained. Lotsch (Deut. med. Woch., June 3, 1920).

OSTEITIS DEFORMANS (PAGET'S DISEASE).—This is a disease described by Sir James Paget in which many of the bones of the body are affected with osteosclerosis. A large proportion of the cases die from malignant disease.

Osteitis deformans, according to Hutchinson, chiefly belongs to the senile periods of life; it may occur in either sex, but is more frequent in men; it often happens to those who have a gouty family history. It consists of a process of osteitis and periostitis, attended by the abundant formation of ill-developed, new bone and the weakening, to some extent, of the old.

It is often in the early stages restricted to one bone, and tends in all cases to become generalized, involving all the bones of the body.

It has no connection with syphilis, although it may be stimulated by it, especially by the hereditary form, and it runs a very chronic course, lasting ten to twenty years. Of itself, it rarely causes death.

It may begin in early adult life and apparently affect only one limb; if, however, in these cases skiagraphs are taken of the other limbs they also are liable to show evidences of the disease.

The writers report 5 cases of osteitis deformans, and in a review of the literature found 208 additional cases. It was found that a much higher percentage of calcium was retained by the patient than in normal individuals, and a lower percentage of sulphur. This condition is opposite to that in osteomalacia in which the body gains sulphur and loses calcium. Since it is known that parathyroid insufficiency leads to disturbance of calcification, it might easily be inferred that decreased activity of the parathyroids is the cause of the retention of calcium, and abnormal use of that element in overproduction of bone less compact than usual. Da Costa, Funk, Bergeim and Hawk (Rep. Jefferson Med. Coll. and Hosp., vi. i, 1915).

[Guaccero describes a case occurring in a woman, aged 55 years in which one tibia

only was affected. As treatment was unavailing he amputated the limb. G. G. DAVIS.]

Endemic fragilitas ossium among the inhabitants of Singly, a village in the Ardennes, with a population of 250 and an annual death rate of 1.5 per cent. Rickets, scurvy, goiter, arthritis, osteomyelitis, tuberculosis, and typhoid are rare in this community, and the average duration of life is high; but 10 per cent. of the inhabitants and many animals suffer spontaneous fracture every year. This singular situation Dr. d'Hôtel attributes to the local drinking water, which by the conditions of its filtration through the soil is deficient in lime-salts. He believes it might easily be remedied by judicious calcic and phosphatic medication of the soil. Editorial (Boston Med. and Surg. Jour., June 6, 1912).

TREATMENT.—In the treatment of the affection considerable comfort can be derived from the use of a proper **supporting apparatus**. Improvement is said to have followed the use of **potassium iodide** and **thyroid gland**, the latter being well known to influence markedly calcium metabolism and general nutrition. Symptomatic treatment is also of use, the patient dying usually of some intercurrent disease.

The writer, in reporting a case, calls attention to the rarity of a disease in the fact that only 3 cases were noted among 38,000 admissions to the New Jefferson Hospital during a period of 7 years. There are only records of 237 cases in the literature. The Wassermann reaction is positive in only one-fifth of the cases. Antiluetic treatment has been tried without avail. Disease of the ductless glands is supposed to be the cause of osteitis deformans. Treatment with a view of influencing the calcium metabolism is being tried, there being at present no satisfactory treatment. The prognosis as regards

cure is hopeless, although as regards life the disease is often compatible with a long and active career. E. H. Funk (*Med. Clin. N. Amer.*, i, 451, 1917).

OSTEOMYELITIS.

Osteomyelitis is an acute inflammatory disease which originates in the spongy and medullary tissue of bone, but not in the compact tissue. It seems to begin at the epiphyseal end of the diaphysis and thence extend down into the joint or up the shaft of the bone.

SYMPTOMS.—It usually begins with a chill, soon followed by severe pain in the affected part, sometimes by redness and fluctuation and severe constitutional disturbance, including a high temperature. In young children the disease may traverse the epiphysal cartilage and affect the neighboring joint. A mild case may be attended by very slight symptoms and proceed to recovery. When the suppurative form is present, however, there may be a prominence over the affected area or a fungous abscess into which the probe readily sinks deeply. Periostitis, which is invariably present, however, may mask the true nature of the case. After the femur and tibia, the vertebræ are the most frequent seats of this affection; an abscess forms, which tends to break down the vertebral column, or bring about meningitis and myelitis by penetration, and thus cause paraplegia. Curvature of the spine is seldom observed, however. Severe cases may end fatally as a result of pyemia or septicemia.

A study of 22 consecutive cases of osteomyelitis of less than 1 year's duration, and the results of treatment 1 year from the date of operation, caused the writer to urge the recog-

nition and prompt energetic treatment of acute osteomyelitis, and recalling the frequency with which the disease is overlooked in the mild cases. Acute osteomyelitis varies greatly in severity, from a mild local infection of a single bone to an overwhelming septicemia, with infection of many bones, and death in a few days, but the milder forms are more common than the severe. Cases seen within a few weeks from the date of onset should be cured by operation except in exceptional instances. One operation is usually insufficient, and 2 or more are often necessary. At the first operation, however, some idea of the prognosis can be obtained and a more or less definite plan for further operations determined upon. Osteomyelitis of the ilium or femur is difficult to treat, and the hope of a cure is much less than when other bones, as those of the forearm or leg, are diseased. Multiple osteomyelitis is exceptionally difficult to cure, but each bone should be treated as if it alone were the only one affected. Infinite pains and patience are necessary to cure any case, and they should be followed up very carefully, especially during the first year, and X-rays taken at frequent intervals. C. C. Simmons (*Boston Med. and Surg. Jour.*, May 10, 1917).

Necrosis or death of the bone may not only be due to osteomyelitis, but, also, as already stated, to periostitis. Whatever be its pathogenic source, however, it ensues as a result of defective nutrition due to interference with the supply of arterial blood. This occurs when the medullary or periosteal lesion that may be present leads to destruction of the Haversian canals. At times the deficient nutrition may be due to numerous emboli originating in a remote region—in the heart, for instance, during endocarditis. Metastatic necrosis is also occasionally witnessed in the course of

infectious diseases, the result probably of bacillary invasion. Under **JAWS, DISEASES OF**, the necrosis brought on by phosphorus has been carefully reviewed. The influence of malnutrition of osseous tissue is readily shown also in dislocation of the astragalus; notwithstanding its replacement and the fact that no external lesions exist, this bone may undergo necrosis. The influence of fractures is also well known, especially when comminution disrupts its trophic supply.

When a long bone is attacked, the whole shaft may be involved or only that part of the diaphysis near the epiphysial line. The periosteum forms new bone over the dead tissues or sequestrum and a suppurative tract or sinus leads from the sequestrum through the surrounding shell of bone to the exterior.

Case of vertebral osteomyelitis in a little girl. There was a spindle-shaped tumor in the left dorsolumbar region, following the direction of the sacrolumbar muscles, and fully 15 cm. long by 7 cm. wide, the lower end on a level with the iliac crest and the top reaching to the eleventh and twelfth dorsal vertebrae. The tumor was hot and fluctuating, slightly painful, but there was no suggestion of a tendency to a gibbus and the spine could be flexed readily. The tumor had developed in the course of fifteen days. Puncture revealed numbers of staphylococci, and the child was at once anesthetized and the focus opened by a long incision, and the cavity cauterized with pure carbolic acid, neutralized with alcohol; drainage was provided. The child was soon cured. Kirmisson (*Presse méd.*, May 12, 1909).

Case of acute osteomyelitis of the spine, the only one on record, according to the writer, terminating in recovery. The patient was a previously healthy man of 28. The spinal affection followed a carbuncle on the back

of the neck while he was traveling, and the frequent change in physicians and a complicating pleural empyema (the fifth on record) aided in retarding differentiation of the true trouble. The osteomyelitis involved the seventh dorsal vertebra, with posterior mediastinitis and irruption into the left pleura and secondary, non-suppurative involvement of the right pleura, with final irruption into a bronchus. Gundermann (*Deut. Zeit. f. Chir.*, March, 1911).

The **X-ray** is of no value in the acute cases but is essential in the later stages as a guide to treatment. The bacterium is a blood-borne organism and in this series the staphylococcus was more virulent than the streptococcus in 10 cases. It varies greatly in severity from a mild local infection of a single bone to an overwhelming septicemia with involvement of several bones and often death. The milder forms are more common. Simmons (*Boston Med. and Surg. Jour.*, May 10, 1917).

Report of 6 extremely severe cases illustrating the fact that the patient may be in a septicemic condition before the local focus manifests itself to any noticeable degree. In 3, the bone in which the condition later developed showed little or no signs of suppuration at the first operation. The staphylococcus aureus was present in each instance. R. A. Walker (*Pract.*, ci, 163, 1918).

ETIOLOGY AND PATHOLOGY.

—Osteomyelitis is most often the result of an infection from one of the pyogenic organisms, either a streptococcus or staphylococcus. Other organisms, such as the pneumococcus, tubercle bacillus, colon, typhoid bacillus, etc., may also cause it. The disease is usually started by some slight injury, particularly in children previously debilitated by the infectious fevers. While osteomyelitis frequently occurs in the course of wounds, compound fractures, and the like, a severe

type occurs, especially in childhood, in which the infection occurs through the blood, there being no wound present.

Bone infection, including chronic osteomyelitis, is produced in the same way as infection of other war wounds. It spreads in two ways: (a) from place to place through the medullary and compact tissue; (b) at a distance, along fissures; penetration through the bone tissue is generally slow and limited. Among the germs which penetrate earliest may be cited the streptococcus, the staphylococcus, the enterococcus, and more rarely the anaërobic microbes. In the microbial flora of subacute or chronic bone suppurations the most frequent are the streptococcus, staphylococcus, enterococcus, and pneumobacillus. Third Internallied Surg. Congr. (Bull. méd., xxxi, 456, 1917).

Childhood and early manhood are most prone to the disease. Cold, traumatism, and overexertion are frequent contributing causes.

An important relationship between osteomalacia and the parathyroids which endocrinologists have long urged as factors in calcium metabolism is again illustrated by the following cases: Schlagenhauser (Wiener klin. Woch., xxviii, 1362, 1915) reported 2 cases of tumors of the parathyroids. One was in a 43-year-old man who had had osteomalacia for 5 years, while the base of the skull showed changes resembling those of osteitis fibrosa. The left lower parathyroid was the size of a plum; histologically it was almost normal. The other patient was a 62-year-old woman who had had osteomalacia for 15 years. The right lower parathyroid was the size of an almond. Histologically it, too, was almost normal. The author recommended operative removal of the hyperplastic parathyroids. In the discussion Maresch said that he had performed autopsies in 23 cases of malacia of the bones. In 10 cases of osteomalacia in women from 58 to 82 the parathyroids were only moderately enlarged, or had merely not atrophied as had the other parenchymatous organs, thus showing a relative enlargement; but there

was no pronounced parathyroid tumor in any of these cases. Bauer recalled that osteomalacia is frequently associated with tetany. Tetany being a sign of parathyroid insufficiency, adenomatous parathyroids might be defective in function; in that case a further removal of parathyroid tissue would be injurious. In a case of osteomalacia observed by Bull and Harbitz (Norsk Mag. f. Laegevid., lxxvi, 417, 1915), a tumor as large as a walnut was found in the left lower parathyroid gland. They recall that similar tumors have been found in other cases of osteomalacia, but they have also sometimes been found in cases without osteomalacia. Harbitz had also observed a case in which there was a tumor in all 4 parathyroids in a man of 75, with paralysis agitans, in which nothing suggested osteomalacia.

The pathology of bone necrosis corresponds to that of gangrene observed in soft tissues. Dead bone is separated from living bone by a line of demarcation of inflammatory origin: a rarefying osteitis. This tends to isolate the dead bone, which then becomes a sequestrum. It may, if small enough, be absorbed after undergoing disintegration; if large, it may persist a long time imbedded in pus, which finally finds an issue. The enveloping shell,—the involucrum,—if it contains a sufficient quantity of pus, becomes perforated, and, this perforation leading to the surface, a fistula is formed. The reproduction of bone in necrosis due to simple inflammatory causes is sometimes remarkable when the subject is strong. Indeed, there is sometimes overproduction, elongation of a limb being thus brought about, especially an injury requiring prolonged sojourn in the recumbent position. In the severe forms of acute osteomyelitis which tend to involve the entire shaft of the long bone attacked the constitutional infection is so severe that

death frequently ensues. A fatal result may be caused by a failure to recognize the true nature of the case early enough.

In 167 cases of osteomyelitis studied by Becker, the joints were affected in 48. The disease was located in the diaphysis of the femur in 45, in the upper epiphysis in 15; lower epiphysis in 3; diaphysis of humerus 18; upper epiphysis 1; lower 4; diaphysis tibia 45; upper epiphysis 3; lower 1; diaphysis fibula 5; lower epiphysis 1; diaphysis radius 4; upper epiphysis 2; upper epiphysis ulna 2; distal epiphyses metatarsals 3; upper epiphyses metacarpals 1; diaphysis phalanges 2, and the lower epiphyses in 1 case.

The writers found 27 cases of osteomyelitis of the sacrum in the literature. The prognosis is graver than for osteomyelitis elsewhere in the spine, the signs of general infection being more pronounced. This is due to the anatomical arrangement of the parts, which causes the infectious focus to be walled in deep and not to manifest itself for some time. The germs thus protected have their virulence exalted and induce general infection with serious phenomena, sometimes even before the focus has been brought to the patient's attention. Operative treatment is indicated at the earliest possible moment to ward off severe general infection or attenuate it. Gaudier and Bertein (*Revue de chir.*, Aug., 1911).

An instance of cranial osteomyelitis following upon intranasal operation for frontal sinusitis was observed by the writer, the first, so far as he knows, to be published. Pus from the brain surface yielded the *Staphylococcus albus* and *aureus* and a streptococcus. Maclay (*Jour. Laryn., Rhin. and Otol.*, June, 1917).

Case of a male, aged 36, who, 21 years prior to his admission to the dental operating room, had had an osteomyelitis in his right femur of such severity that the leg was amputated at the hip-joint. During the years following, the patient had more than 30 operations on various

parts of the body. Osteomyelitis had been found in the left leg, elbows, arms and inferior mandible. Radiograms of the teeth were made and 6 lower incisors extracted. These teeth had probably been the focus of infection for more than 20 years. M. H. Feldman (*Dental Cosmos*, lx, 147, 1918).

Osteomyelitis of the spine is usually acute, being marked by severe pain in the vertebral region. Appearance of a tumor next the vertebral column usually quickly follows. The temperature is, as a rule, about 100° or 101°. The abscess, if opened, reveals staphylococci in great abundance. In one instance an operation was performed 2 days after the onset and consisted in laminectomy and drainage of the epidural abscess. Death is due in half the cases to penetration of the pus into the spinal canal. On the whole, the prognosis is very grave, much more so in osteomyelitis of the vertebral bodies than of the laminae. Incision with drainage might suffice, but a laminectomy is preferable as it insures better drainage. Removal of the diseased bone would increase the operative risk. Grisel's statistics show, among 40 cases, 23 recoveries and 17 deaths. L. Luzoir (*Presse méd.*, xxvi, 378, 1918).

TREATMENT.—When a joint is affected it may first be **aspirated**; if the effusion is marked or if the case is sufficiently alarming the articulation may be **laid open**, washed out, and drained or even the joint **resected**.

Forty cases of acute and chronic osteomyelitis, compound fractures and joint tuberculosis have been treated by the writer by the **Carrell technique**, all responding remarkably well, with the exception of 2 cases of tuberculosis. In his experience it has been possible definitely to sterilize suppurating infections of the bones and joints and see them heal without any evidence of pus and

without sinus formation. This occurred, in all the cases not still under treatment. He also observed 2 entirely new phenomena:—the growth of granulation tissue from the bone itself and a peculiar form sequestration. Hawley (*Amer. Jour. of Orthop. Surg.*, Aug., 1917).

Thyroid gland, owing to its power to increase the opsonins and enhance the germicidal and antitoxic activity of the blood, is indicated in osseous disorders in which pathogenic germs take an active part. In osteomyelitis the desiccated thyroid gland should be given in 2-grain (0.12 Gm.) doses three times daily. This measure hastens the curative process or initiates it in chronic cases. Sajous (*Monthly Cyclopedia and Med. Bull.*, April, 1912).

In case the long bones are involved **free incision and drainage** should be resorted to in order to cut short the systemic disturbance and allow time for the periosteum to become sufficiently thickened to allow of its being pushed aside while removal of the affected bone is being accomplished.

In some cases **longitudinal section** with Hey's saw and **curettage** are required to totally evacuate the contents; a small trephine or gouge and mallet may be used when the accumulation is not readily accessible and the purulent material is thickened.

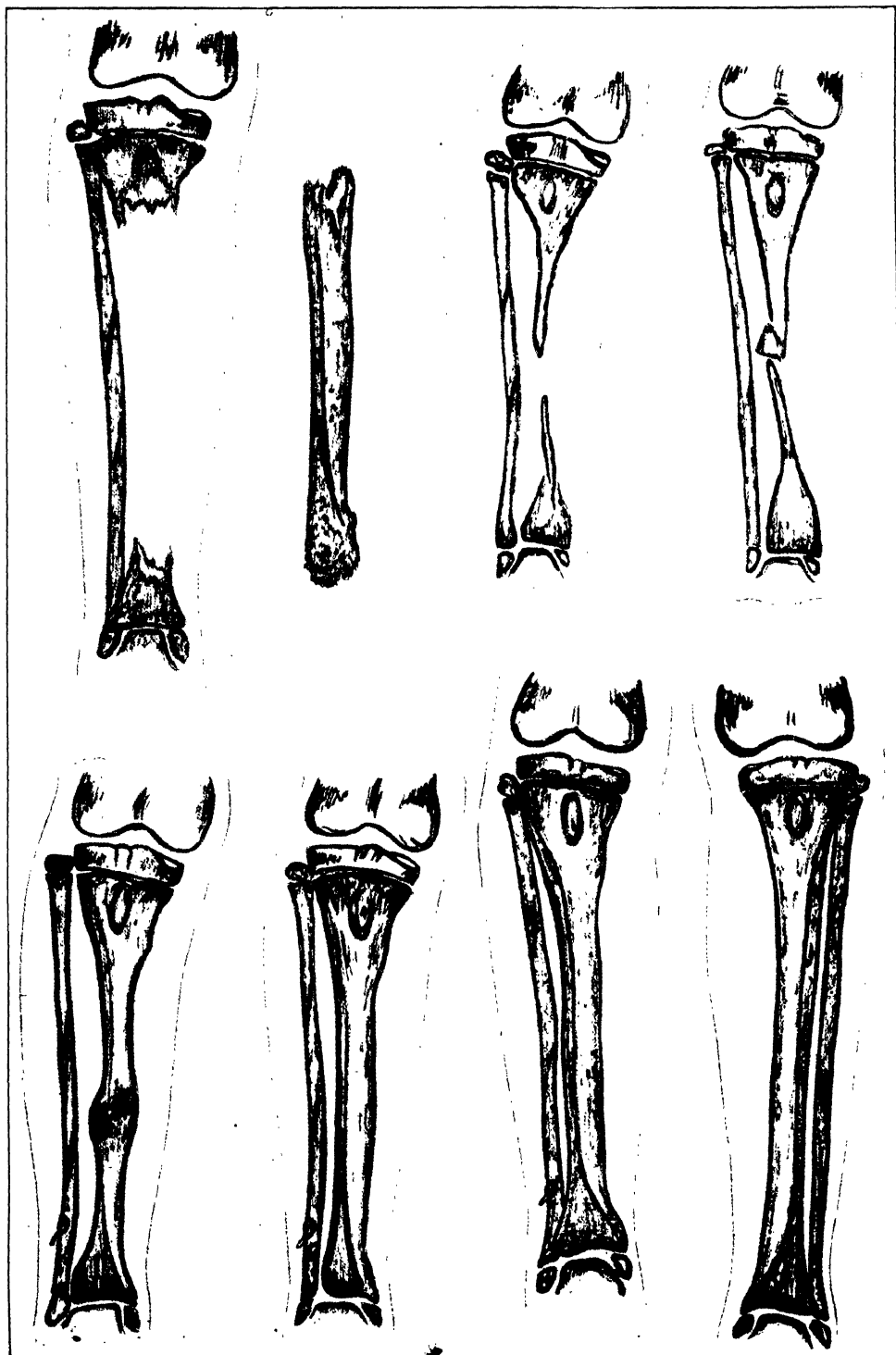
Case of osteomyelitis of the rib complicating typhoid cured by the injections of an **autogenous vaccine** which the writer prepared from cultures of the typhoid bacillus found in pus discharging from the lesion. R. C. Rosenberger (*N. Y. Med. Jour.*, May 13, 1911).

A patient cured in 3 weeks by the **vaccine therapy**, the case—a typhoidal suppurating bone process that had dragged along for 2 years—having been subjected to 7 futile operations. The cure was complete in 1 week in another case after 11 months of the

affection and 3 operations. Improvement amounting to a cure was obtained also in 2 weeks in processes of 6 to 12 months' standing in other cases. It failed only in 1 case, but the removal of a sequester initiated the healing process. P. Emile-Weil (*Bull. de l'Acad. de méd.*, Jan. 23, 1917).

Necrotic sequestra are readily recognized by the grating sensation transmitted through the probe. They should be removed when free in the cavity, which their mobility will readily indicate. It is usually necessary to enlarge the opening. When the piece is large a gouge or chisel is necessary to thoroughly remove all dead bone. The Esmarch tourniquet, but not the bandage, should be used to avoid hemorrhage, the limb being first elevated to drain it of blood.

When after the removal of dead bone in old chronic cases a long and deep gap is left, an effort should be made to encourage the production of new bone. Bits of human bone will grow and develop if the chips are thoroughly aseptized, and sometimes it is possible to make the transplantation from the bone of a living animal. **Animals' bone, ivory, and other aseptic organic materials** can be made to become healed in and absorbed, capsulated, and partially or totally substituted by the growing bone in which they are planted and to which they furnish the irritation for osteogenesis. These procedures, however, are so liable to fail that Mosetig-Moorhof advised filling the cavity, which had first been thoroughly disinfected and dried with a **wax mass** composed of spermaceti wax, iodoform, and oil of sesame. In some cases this heals in and the wound closes by primary union.



Regeneration of the tibia in a boy. (*J. A. Hutchinson.*)
Montreal Medical Journal.

New method of treating old cases of osteomyelitis of the ribs and long bones. The writer makes an adequate flap incision; removes every vestige of the diseased tissues under the guidance of the eye; closes the wound so as not to permit any dead space in the resected cavity, and implants the skin-flap. He uses no suture material except ligatures for arteries, and leaves the wounds widely gaping. He reproduces epithelium of granulating surfaces with skin-grafts. He has thus been able to cure nearly all the cases which had previously undergone operation and failed and which could not be cured by injection of bismuth paste on account of sequestra. Beck (Trans. West. Surg. Assoc., Dec., 1916; Surg., Gynec. and Obstet., Feb., 1917).

Case of regeneration of the shaft of the tibia in less than two years in a boy aged 12 years, admitted March 11, 1908, suffering from a large swelling in the front of the right leg, and a small swelling in the right wrist and forearm.

The result was obtained by means of the **Mosetig-Moorhof plumbage** method. The annexed plate shows the progress of the osseous regeneration as indicated by X-ray plates. J. Alex. Hutchison (Montreal Med. Jour., July, 1910). (See illustration.)

Usually, however, some discharge ensues and a certain proportion of the wax comes away, but some still remains in and heals in place. Even additional wax may be injected. By this means the healing of these bone cavities has been very much expedited. In the treatment of the sinuses connecting with bare bone, but without sequestra, Beck, of Chicago, has advised the injection into the sinus of a mass consisting of soft white vaselin and bismuth subnitrate or subcarbonate. This method of treatment of obstinate bone sinuses has been amply tested and proven beyond dis-

pute to be of the greatest value. (See article on BISMUTH, this volume.)

A new method of treating osteomyelitis and bone necrosis, which is very simple, consists of making a number of small holes in the bone, perforating somewhat like a grater, over the entire exposed part from 3 to 4 mm. apart. Their depth depends on the thickness of the necrosed bone or, in the case of osteomyelitis, on the thickness of the external part of the bone as far as the medulla. In cases of necrosis, trepanation of the bone ought to be done without an anesthetic because if the bone is really dead there is no sensibility. In the cranium, of course, only the external table is perforated. The perforations facilitate the penetration of granulations into the bone so that in a short time they cover all the exposed part and skin may be grafted from the vicinity. He used this method successfully in 7 cases, 4 of necrosis of the tibia, 1 of cranial denudation, and 2 of acute osteomyelitis of the femur. While he is not yet able to report a definite recovery, the necrosed bone in all cases has been resorbed and its place has been taken by bone cells of new formation. A. L. Soresi (Arch. di ortop., xxxiv, 338, 1919).

The writer describes his late experiences in the treatment of over 2000 cases of infected bone wounds treated at U. S. Army General Hospital No. 28, Fort Sheridan, Illinois. Primary débridement had been performed in all instances and in the majority 3 or 4 sequestrotomies had been done before the patient arrived. In the severe types either **Carrel-Dakin treatment** or a wound pack of gauze saturated in **Dakin's fluid** was used. Nearly every case required an operation of some kind, usually a **sequestrotomy**, and proper drainage. In cases of discharging sinus without marked general disturbance, more than 70 per cent. of the cases showed sequestra and 40 per cent. had cavities which would not heal perma-

nently. **Sequestrotomy**, followed by complete **cauterization** of the bone cavity, gave very satisfactory results. In cavities near joints, where this method is not applicable, the use of **pedunculated flaps** of healthy and well-vascularized muscle is recommended. In several cases in which the lower end of the femur was partially lost the bone cavity was packed with **Dakinized gauze** until the bacterial count was reduced to a minimum, when a large flap of the vastus muscle was turned down and pressed into the cavity. The results were good. E. W. Ryerson (*Jour. of Orthop. Surg.*, ii, 499, 1920).

In cases in which the bone is extensively diseased, or gangrenous osteomyelitis is present, or when through extensive suppuration the patient's life is clearly endangered, **amputation** is indicated. This is especially the case when a long bone is implicated. In such a case, however, the bone should be removed entire, section in its continuity being, as a rule, followed by recurrence.

In children osteomyelitis of the long bones begins in the ends of the diaphyses, principally in the weight-bearing bones. The early measures should include **removal of bone** for purposes of drainage only, the infected medulla being fully uncovered without doing unnecessary injury to the periosteum or endosteum. Considering the power of regeneration of periosteum plus endosteum, early complete resection of a shaft is not advisable; therefore, total resection later should be reserved for cases of total necrosis. Homans (*Annals of Surg.*, March, 1912).

The gouge and chisel should not be used, being liable to cause remote fissures or at least to deaden the bone tissue and favor infection and thrombosis. An electric drill is much preferable. Provisional hemostasis is indispensable. X-ray negatives taken from front and side must

be constantly under the eyes of the operator; röntgenoscopy is not sufficient to disclose the finer lesions of the osteitis. Curetting is a blind procedure, apt to inoculate sound tissue while neglecting diseased points. The author makes no attempt to fill up the cavity, but lines it with the skin loosened up around and drawn down into the cavity and fastened there, then applying a compressing bandage, before tying the provisional hemostasis. This dressing is removed on the fourth or fifth day. If slight infection results, he irrigates with **Dakin's solution** and completes the cure with **heliotherapy**. If the skin cannot be drawn down to cover the cavity completely, the gap is filled with **Reverdin grafts** toward the end of the second week, recommencing a week later exposures to **sunlight**. Jean (*Presse méd.*, Sept. 5, 1918):

RACHITIS.

Rachitis, or rickets, is a disease of infancy and childhood due to malnutrition of the osseous structures.

SYMPTOMS.—Nocturnal restlessness, night-sweats (especially of the scalp), enlarged abdomen, and phosphaturia are the early symptoms of this affection. The joints not infrequently become painful, and the child cries when roughly handled. The osseous involvement appears soon afterward and consists of epiphysal enlargements, of which the end of the tibia, radius, the ribs, and the vertebræ are the most frequent seats. The costal disorder is followed by the deformity usually called "pigeon-breast." Beading of the ribs, also called the "rachitic rosary," is quite common. The frontal eminences and other portions of the facial bony framework are often enlarged; the fontanelles are frequently patent and the growth is often impaired. Such children are usually late in walking

and susceptible to catarrhal affections of the entire respiratory tract, nose, throat, and lungs.

In 400 consecutive infants under 2 years of age, examined as medical outpatients of the Infants' Hospital, by Morse, for evidence of rickets, 80 per cent. showed more or less marked signs. A rosary was presented in every case; it was the only symptom in 40 per cent. It was accompanied by one other symptom in 20 per cent: often delayed dentition; next, enlargement of the cranial eminences. Delayed dentition occurred in more than 50 per cent.

Of the more frequent mistakes in diagnosis, one is the failure to recognize inflammatory and bloody effusions under the periosteum, and this is undoubtedly the cause of the use of the term acute rickets. Another is mistaking the bone changes of congenital syphilis for those of rickets, and still a third is that of considering the pseudoparalysis of rickets as essential paralysis. Infantile scurvy may complicate rickets, but the two conditions are distinct. Children rarely die of rickets *per se*; some intercurrent disorder is the cause of death, especially lung disorders. J. W. Van Derslice (Jour. Amer. Med. Assoc., Oct. 15, 1910).

In an examination of 1000 school children in the East End district of London he found 80 per cent. showed evidence of rickets in their teeth. The great majority of the children were of Jewish parentage. The teeth commonly affected are the central and lateral incisors, the tips of the canines, and the crown of the first molars. J. L. Dick (Brit. Jour. Child. Dis., Nov., 1916).

Deformity of the spine and other bones occurs as a result of the softening. Probably the most pernicious effect of this condition is its influence upon the female pelvis, distortion of which when adult life is reached impedes and sometimes totally prevents parturition. Sometimes a marked

groove—Harrison's groove—is seen on each side of the xiphoid cartilage; also a marked depression at the same place called funnel chest or the trichter-breast of the Germans. It is supposed to be due to the traction of the diaphragm on the weakened ribs.

Abdominal atony and distention is an important feature of rickets: It affects the gastrointestinal motor functions both as to excretion and secretion; it interferes with the circulation and produces passive portal congestion; it produces functional and anatomical alterations in respiration, and, finally, it causes eversion of the costal arch. Ewart (Brit. Med. Jour., Oct. 13, 1906).

The writer describes two sorts of digestive troubles in patients suffering from rickets: the one, prodromic or initiative, usually consists of recurrent gastrointestinal catarrh, more rarely of a spasmodic dyspepsia with repeated vomitings; the other, met with in confirmed rickets, consists of a special form of atonic dyspepsia, with large, flabby abdomen. A. B. Marfan (Presse méd., Nov. 18, 1908).

Slight anemia is the rule with rachitis, and the blood-findings on the whole are characteristic, though no parallelism with the severity of the case can be said to exist. The leucocytes are slightly increased in number; all the mononuclear forms are increased and show many atypical shapes. Myelocytes are found in the severe forms, and the nucleated reds may reach extremely high proportions. Aschenheim (Deut. Archiv f. klin. Med., Bd. cx, Nu. 5-6, 1912).

ETIOLOGY AND PATHOLOGY.

—The predominating features are that the epiphysial ends of the bones are thickened, and that the bony tissue which forms is deficient in lime-salts. Hyperemia of the osteogenetic tissues first causes growth of the cartilage at the epiphysial line, which becomes enlarged and irregular in histological

structure. The bones are so soft that they can easily be cut, and the ligaments are elongated. When curvature of the spine ensues, we have *scoliosis* (see SPINE, DISEASES OF) or *lordosis*; the pelvis may also become *kyphotic*. The skull may become thinned: a condition recognized as *craniotabes*, and its enlargement forms the physical basis of hydrocephalus (*q.v.*). Many of the deformities considered under ORTHOPEDIC SURGERY are due primarily to rachitis.

There are four characteristics which distinguish syphilitic rickets: (1) its early appearance; it is either congenital or appears during the first three or four months of life, and this characteristic the writer considers the most important; (2) the predominance of cranial lesions; (3) the usual coincidence of a very marked anemia; (4) the frequent presence of a chronic hypertrophy of the spleen, which he considers, likewise, to be a very important symptom. Marfan (*La Semaine médicale*, Oct. 2, 1907).

Poverty, unhygienic surroundings, deficient food, artificial infant foods, dampness, insufficient exercise and defective ventilation, etc., represent the etiological factors which environment procures. Hence the greater prevalence of rickets in crowded cities, especially those of the poorer countries of Europe, and among our negro population. It usually appears as soon as the child tries to walk, and may be congenital. Certain rare cases occur in young adults, which seem to be due to a somewhat similar cause.

Under physiological conditions the amount of lime taken up by infants may be insufficient, both when they are nursed and, more often, when they are fed artificially, and a reduction of the amount of lime in the

milk below the physiological minimum is productive of pathological changes in the bones, as has been shown by experiments on animals. Schabad (*Berl. klin. Woch.*, May 3, 1909).

Rachitis is a disturbance in the lime metabolism leading to increased excretion of the lime-salts into the intestine. The rachitic bone changes are the consequence of this general metabolic disturbance. W. Dibbelt (*Münch. med. Woch.*, Oct. 11, 1910).

Perversions of the functions of some of the ductless glands, especially the thymus and adrenals, have also been thought to underlie the development of the disease.

Attention has been devoted to the rachitic changes of the bones in tetany of children, and the view has been expressed, by Kassowitz, that the tetanic spasms are the direct sequelæ of the rachitic process in the bone. It is now assumed that the two phenomena are probably directly related to the changes of the parathyroids. A study of the question led the writer to conclude that an important part among the non-nervous symptoms of the general disease, tetany, is played by chronic affections of the osseous system, which have not so far been sufficiently appreciated, especially in adults. Tetany must accordingly be included among the affections of glands having an internal secretion; the bone-marrow tissue likewise belongs to these organs. Schueller (*Wiener med. Woch.*, Nu. 38, 1909).

A quantitative modification of the bone-marrow is the essential feature of rickets. The qualitative changes are like those encountered in ordinary infections, the writer states, but the remarkable proliferation of the bone-marrow seems to be specific for rachitis. The bone-tissue also displays a tendency to evolutive dystrophy, which is also evident, although to a lesser degree, in all the tissues. This dystrophy may even involve the suprarenals, thymus, etc.,

but the anomalies in the glands may be regarded as the result of the nutritional disturbance responsible for the bone lesions, rather than as themselves the cause of the rachitis. V. Hutinel (*Arch. de méd. des enf.*, Feb., 1910).

Spontaneous rickets shows exactly the same symptoms as Basch, Klose, Vogt and Matti attribute to thymusectomy, if one except the adipose stage of Klose and Vogt. Yet removal of the thymus from animals does not make them more susceptible to spontaneous rickets, and if they develop it, they do so at the same time and in the same manner as the controls. Thymusectomy of itself does not appear to cause any symptoms. Renton and Robertson (*Jour. Pathol. and Bacter.*, Dec., 1916).

TREATMENT.—In the treatment of rachitis the first essential is to make a positive change in the diet of the patient. The necessity for this is not always appreciated. It is certainly evident that as the child has developed the disease under its previous diet a change cannot be for the worse, and will probably be for the better. Fresh and nutritious foods should replace the ordinary diet, and all prepared foods for children should be strictly avoided. Siegert in a study of 2152 children showed that among them rickets occurred almost exclusively in the artificially fed infants unless there was an inherited predisposition.

The writer has sought to determine the relation of the incidence of rickets to the varying conditions under which lactation is exercised and to the duration of this function. He studied 200 children, dividing them into four classes, according to their early feeding: (a) Breast feeding; reared wholly on the breast for from eight to twelve months. (b) Hyperlactation; reared wholly or mainly on the breast for over twelve

months. (c) Mixed feeding; partly on the bottle, and partly on the breast. (d) Bottle feeding; entirely on the bottle. He found that rickets was appreciably more marked among children "breast fed" for over eight months (including those with hyperlactation) than among other children, and, as these breast-fed children were, in a large majority of cases, born of mothers who had undergone greater lactational strain, and as this lactational strain does only to a slight extent predispose the infant to rickets, consequently one is forced to consider the composition and fitness of the maternal milk in these cases. A. Dingwall-Fordyce (*Brit. Med. Jour.*, April 28, 1906).

The diet is of the first importance. In breast-fed children it becomes necessary to influence the mother in such manner as to make her milk suitable for the child. In many of the cases it becomes necessary to supplement the breast by suitable artificial foods. Good hygiene with plenty of fresh air is a prerequisite. No diet can be set down that can be recommended in these cases. Van Derslice (*Jour. Amer. Med. Assoc.*, Oct. 15, 1910).

In the children's clinic at Petrograd where his extensive research on rachitis has been carried out, the writer studied the results of the **mixed diet**—with very little milk—advocated by Czerny-Keller, comparing the metabolic findings with those on a diet of unlimited milk and bread, both in periods with and without cod liver oil. The children seemed to do a little better on the Czerny-Keller mixed diet only when **cod liver oil** was given with it, showing that this diet lacks essential therapeutic efficacy, while the children are unable to utilize it as well as plain milk and white bread. Schabad (*Russky Vrach*, xv, No. 45, 1916).

Codliver oil has long been considered as most useful. There is no remedy which at all approaches it in

efficiency. It should be given internally and rubbed into the skin externally. The **compound syrup of the hypophosphites and lactophosphate of lime** are sometimes of service, but codliver oil is almost a specific.

The writer's observations confirm Schabad's conclusions concerning the specific action of codliver oil upon the metabolism in rachitis and the convulsions so often associated with rachitis. Five personal cases of rachitis with marked craniotabes; remarkable benefit followed the daily administration of 25 Gm. (6½ drams) of **codliver oil** for three to six weeks. **Phosphorus** undoubtedly enhances the action of the codliver oil when given in a mixture of 0.01 part of phosphorus to 250 parts of codliver oil, a teaspoonful being given five times a day to the severest cases. Rosenstern (Berl. klin. Woch., Bd. xlvii, S. 822, 1910).

In a research the writer found that in the progressive phase of rachitis, phosphoric acid is evacuated in the feces much more than in normal conditions. Under **cod liver oil**, as improvement progresses, the evacuation by way of the intestines becomes materially reduced. With spontaneous improvement, on the other hand, the reduction in the output occurs in the evacuation through the urine. He regards this fact as demonstrating that the cod liver oil ensures better utilization of the food, improving absorption, but not influencing the disease process directly. He warns that it takes over 3 months for the improvement to reach an appreciable stage. Schloss (Berl. klin. Woch., Dec. 25, 1916).

Cod liver oil having long been regarded as the sovereign remedy for rickets, the writers tried it as a prophylactic in this disease. About 90 per cent. of the colored babies are subject to rickets in a negro community in New York, known as Columbus Hill. This district, having a population of about 9000, has the highest mortality of any in New

York. At the end of 6 months 49 out of a series of 80 babies had been given the full treatment. The development of rickets was prevented in more than four-fifths of the infants who received the oil for 6 months, and in more than one-half of those who were given it for 4 months. Hess and Unger (Jour. Amer. Med. Assoc., Nov. 1, 1917).

The disease has been attributed to lack of fresh air; therefore, hygienic measures, such as **outdoor life** (the patient being wheeled out in a carriage, if need be), **salt-water bathing**, and residence on the **seashore**, are of great value, but unfortunately the latter is seldom within the means of the patient. Rickets is essentially a disease of temperate and cold climates, and almost unknown in warm regions, where people do not shut themselves up in close rooms.

Rickets may be said to affect at least 50 per cent. of the children of industrial populations. While not directly fatal, it increases susceptibility to the respiratory complications of measles and whooping cough. Normally fed young dogs could be made rachitic simply by confinement and lack of exercise, while dogs fed on a diet poor in fat but allowed to exercise developed diarrhea and inarasmus, not rickets. In a statistical study of the dietetic and home conditions of over 500 rachitic children, the author found the main etiological factors, in the order of their significance, to be improper housing, absence of facilities for open air life, and imperfect parental care. Poverty *per se* did not seem a factor of any importance. Most of the rachitic children were as suitably fed as the non-rachitic. The amount spent on rent, however, was distinctly greater in the non-rachitic than in the rachitic family. Where rachitic and non-rachitic occupied the same houses, neither the number of stairs up, the exposure, nor the ven-

tilation seemed to affect the frequency of the disease. Quite otherwise was it, however, when the number of persons to an apartment and the general cleanliness and care of the home were considered. With the markedly rachitic children, 3.93 persons inhabited each apartment; 3.0 was the average for non-rachitic families. The average air space for markedly rachitic families was 422 cubic feet per person, for the mildly rachitic, 483 cubic feet, and for the non-rachitic families, 625 cubic feet. Nearly 50 per cent. of the rachitic children were admittedly not taken out for exercise, and only 30 per cent. seemed to be sufficiently exercised in the open air. Of the healthy non-rachitic children, 86.5 per cent. were properly exercised in the open, and only 4 per cent. did not receive the necessary airings. The seasonal incidence of the disease—spring rather than late summer or autumn—is undoubtedly due to this open air factor. The incidence of rickets would seem to be a question of economics. L. Findlay (*Glasgow Med. Jour.*, May, 1918).

The presence of iodine in codliver oil, and also in the internal secretion of the thyroid, suggested the use of **thyroid gland**. In the few instances in which it has been tried so far, it seemed to prove very beneficial. **Thy-mus gland** and **adrenal gland** have also been tried, but with less pronounced benefit.

The writer obtains the best results in rickets by a combination of **nucleinic acid** and its salts, especially the sodium salt, with the **glycerophosphates of calcium**. Sittler (*Münch. med. Woch.*, July 16, 1907).

Rickets is found in 92 per cent. of premature and twin infants. This is due to a deficiency of calcium at birth. Calcium in the form of **tricalcium phosphate** must be added to the usual treatment. Huenekens (*Journal-Lancet*, Dec. 15, 1917).

To forestall or prevent the occurrence of deformities and to correct them the child should be kept off its feet and **splints** or apparatus applied. Splints of the simplest character, such as those made of pasteboard and bandaged on, are of considerable service. Simple supports for the back are also valuable. If the disease is marked, deformities will occur, even though the child does not stand on its feet.

Two measures are of great value in the treatment of abdominal atony of rickets: 1. **Massage of the abdomen**, which invigorates the muscles, reduces the distention, disperses visceral congestion, and assists respiration. 2. The use of an **elastic abdominal belt**; this is automatic, gives lateral support to the weak abdominal parietes, improves the distribution of the blood, and corrects the apparent oligemia, and is of the greatest assistance to the respiration. Above all, it stimulates the growth of the abdominal muscles. Ewart (*Brit. Med. Jour.*, Oct. 13, 1906).

The changes in the bones and the muscular atrophy are to be prevented if possible by suitable **gymnastics** and by **stimulation** of the circulation with regulated **massage** and **baths**. After the condition has developed, the methods must be somewhat different. If the stools are loose and contain mucus, massage is contraindicated. When there is constipation with meteorism, **abdominal massage** should be started, and this is especially true in those cases where there are weakness and atrophy of the abdominal muscles. Besides having an influence upon the abdominal muscles, such massage regulates peristalsis and improves the secretory powers of the stomach and intestines. Physical therapy also improves the function of the skin; by thermic stimulation a prompt reaction of the capillaries is obtained. The **air bath** is suggested as an important therapeutic measure. At first its duration is from three to

four minutes, and this is gradually increased during the course of a month to half an hour. It is to be followed by a vigorous rubbing, until the skin is red. During the summer it may be given out of doors, in a place which is protected from the wind. If possible, sunlight should be a part of the air bath. By this method the secondary anemia of rickets is most speedily cured. Kirchberg (*Der Kinderarzt*, Dec., 1911).

OSTEOMALACIA (MOLLITIES OSSIIUM).

This is a softening of the bones in adults which occurs most frequently in nursing-women.

SYMPTOMS.—The early symptoms of this disease are often obscure, the pain and muscular weakness complained of often leading to a diagnosis of rheumatism or suggesting some disease of the spinal cord. The progressive softening of the bones, however, soon leads to deformities, which gradually increase in degree and extent. The bones of the spinal column and the pelvis suffer most, the latter giving rise to great decrease in the pelvic diameters and the former leading to decrease in height. The patient assumes a waddling gait through the pelvic changes. Fracture of the long bones from muscular action is often observed. Death is usually due to exhaustion or pulmonary disease. In rare cases the disease becomes arrested.

DIAGNOSIS.—While rheumatism may be suggested early in the history of a given case, a diagnostic point of importance soon supervenes to indicate the true nature of the trouble, namely, the numerous painful areas. The sex of the patient, the possible presence of pregnancy, the presence of lime-salts in the urine, and the

peculiar deformities witnessed, all serve to identify the affection.

ETIOLOGY.—The disease is almost always observed in women. Fehling has wrongly asserted that it never occurs in men. Though most authorities state that it does not attack childhood, it has been observed as early as the twelfth year.

Case in boy 12 years of age who was suddenly seized with a pain in the left leg. There were no local manifestations, but the constitutional symptoms of fever were well marked. His temperature ranged as high as 105°, and was accompanied by a rapid pulse and marked delirium. A slight redness appeared over the upper extremity of the left tibia. All the symptoms of inflammation increased and an incision was made over this area, demonstrating a quantity of pus beneath the periosteum. This operation relieved all of the more violent symptoms, but in a few days induration and redness appeared over the end of the tibia, and incision was made near the inner malleolus. Another opening was made near the middle of the shaft. The sinuses persisted and a more extensive operation was undertaken; the entire medullary canal was opened and curetted. A rapid recovery ensued. S. L. Taylor (*L. I. Med. Jour.*, April, 1912).

It is usually ascribed to defective osseous nutrition, through disorder of the trophic nerves, to deficiency of lactic acid, and to disease of the genital apparatus; but none of these may be said to have been positively demonstrated.

The writers have previously been led, by a study of the etiology of osteomalacia, to the conclusion that the starting point of the disease is an increased catabolism of bony tissue due to a need of calcium salts elsewhere. The tendency of physiological activity to overproduction

which is responsible for the production of antitoxins and acquired immunity is also an important factor in osteomalacia in leading to the long-continued increased catabolism of calcium after the original need has ceased. The present communication concerns a rare case of non-puerperal osteomalacia which offers an opportunity to test the soundness of the theory. The condition was one of osteomalacia following the appearance of multiple bony tumors. A complete metabolism experiment of ten days' duration, in which the intake and outgo of nitrogen, calcium, magnesium, sulphur, and phosphorus was determined, showed a definite loss of calcium and retention of all other elements. The retention of sulphur and magnesium was greater in proportion than that of nitrogen and corresponded to a growth of tissue richer in these elements than any of the soft tissues—a tissue such as bone. The retention, moreover, taken together with the loss of calcium, is in accord with the conception of osteomalacia as a process in which the bone is undergoing metabolism, but in which the new bone laid down is an osteoid tissue poor in lime-salts, but richer than normal in magnesium. The bony tumors preceding the osteomalacia supported the conception that the starting point of the disease can usually, if not always, be traced to a demand for calcium salts, while the continued excretion of an excess of calcium when the bones really need this element suggests the importance of the physiological tendency to overproduction in bringing about bone softening. McCrudden and Fales (Arch. of Int. Med., March, 1912).

PATHOLOGY.—The morbid anatomical changes observed in osteomalacia are not always the same. In some cases bone absorption is the chief element; in others the disappearance of earthy salts; but decalcification appears to be the earlier process.

The writer studied osteoporosis and osteomalacia in 26 women of 19 to 72 years of age, 23 of whom were of the climacteric and postclimacteric age. They were of the poorer class, with 16 having admitted deficient nourishment, namely, potatoes, turnips, thin soup, war bread and the small meat ration. Milk, eggs, cheese and butter were lacking. Most of the women weighed under 110 pounds. In many, emaciation was far advanced; 7 had had rickets, 15 presented curvatures of the spine. Some were confined to bed. Spontaneous fractures had occurred in 10 cases. The writer's diagnosis was osteoporosis from undernutrition (lack of protein, lime and phosphorus). Alwens (Münch. med. Woch., Sept. 19, 1919).

As the morbid process progresses the organic portions are absorbed. In the long bones the medullary cavity is found enlarged, and the whole bone more cancellous, and as the disease advances the periosteum is stripped off, and a number of openings are seen, from which a clear fluid exudes. Fehling regards increased vascularity and friability of the ovaries as characteristic of the disease, and a hyaline degeneration of the arteries has been observed. Winkel and Kleinwachter deny that these changes are characteristic. There is a growing tendency, however, to attribute the disease to some disturbance of the ductless glands.

The aggravation of the symptoms during menses and pregnancy is certainly due to the increase in size and augmented secretion of the ovaries, although the ovaries themselves are not directly responsible for the osteomalacia. Besides removal of these organs, **phosphorus** and **suprarenal preparations** and ovarian antibodies are logically indicated in treatment. In a recent case a III-para of 27, eight months pregnant, presented symptoms of osteomalacia. Castra-

tion was advised, but refused. After the childbirth the symptoms subsided, but returned again at the next pregnancy in so severe a form that the ovaries had to be removed. To insure completeness the tubes were resected at the same time. The expected abortion did not occur, and seven months later a normal child was delivered. The symptoms of osteomalacia subsided immediately after the **castration**. Cramer (Münch. med. Woch., April 13, 1909).

In a case of osteomalacia observed by the writers, a tumor as large as a walnut was found in the left lower parathyroid gland. They recall that similar tumors have been found in other cases of osteomalacia, but they have also sometimes been found in cases without osteomalacia. Harbitz also observed a case in which there was a tumor in all 4 parathyroids in a man of 75 with paralysis agitans in which nothing suggested osteomalacia. Bull and Harbitz (Norsk Mag. f. Laegevid., lxxvi, 417, 1915).

The action of no one gland or glands may be considered as the causal factor. The conception of osteomalacia as an exaggeration of normal bone catabolism seems worthy of consideration, and it is hoped that further studies may indicate an influence of the endocrine glands upon such metabolism. W. H. Nadler (Endocrinology, Jan., 1917).

As evidence of polyglandular endocrine insufficiency in osteomalacia the author enumerates the following symptoms: Osseous gracility, hyperplasia of the bone marrow, decalcification, sensitiveness of the periosteum, which is markedly influenced by exhibition of adrenalin; muscular dystrophies; psychic disturbances; increased reflexes, spasms, tremor, pyrexia, hyperidrosis, paresthesia, disturbances of metabolism, and changes in hematopoiesis. As to lesions of the endocrine organs, insufficiency of the hypophysis and suprarenals has been met with as evidenced by the favorable results from exhibition of extracts of these glands.

The hyperfunction of the genital glands is demonstrated by the influence of castration. The parathyroids are often hypertrophies, but this is common in all kinds of calciprive diseases. Naegli (Münch. med. Woch., May 28, 1918).

TREATMENT. — Phosphorus, which is of no particular value in rickets, is sometimes very effective in this disease. The most successful method is that of Kasminski, who gives it with codliver oil. He first gives 2 teaspoonfuls a day of a mixture containing $\frac{1}{3}$ grain (0.021 Gm.) of **phosphorus** and 3 ounces (90 Gm.) of **codliver oil**. He then gradually increases the daily dose until 6 teaspoonfuls are taken daily, the patient being closely watched. The mouth must be kept scrupulously clean. The treatment lasts from four to fourteen months. Mosengeil in 1874 first used **phosphorus** in these cases.

The non-puerperal form of osteomalacia, the osteomalacia senilis and tarda, is not rare and deserves to be better known. Osteomalacia senilis and tarda is curable by **phosphorus** in almost all cases if the treatment is maintained. Castration should not be performed in such cases without trying previously an energetic and long-continued treatment with phosphorus. H. Curschmann (Med. Klinik, Oct. 8, 1911).

Another method tending to favorably influence the disease is **removal of the ovaries**, as proposed by Fehling. This has frequently been followed by success.

In 1901, A. I. Danilevsky discovered a substance in milk which he designated as "**phosphatic albumin**," precipitated from the milk whey by alkalies. It is apparently in loose combination with the phosphates. It gives no reaction with Millon's reagent, and is therefore not a true albumin, but an albuminoid, according to Vilenkin (N. Y. Med. Jour., June 17,

1916). Slovtsoff (Roussky Vratch, Feb. 6, 1916) experiments leading to the conclusion that phosphatic albumin has a marked effect on the development of the teeth, and in young animals, also on the long bones. Coincident with more rapid growth, a beneficial effect on the bone marrow is also observed. Apparently this substance in milk belongs to the bone-forming elements.

Case of osteomalacia cured by **removal** of the sound **ovaries** through the vagina. One year later monthly hemorrhages appeared resembling menstruation and the symptoms of osteomalacia recurred. The bleeding was traced to a polypus in the uterus; after its removal the hemorrhages ceased and the symptoms of osteomalacia subsided also. Theilhaber (Zentralbl. f. Gynäk., Bd. xxx, Nu. 5, 1906).

Case of a woman of 41 who had borne eight children, osteomalacia developing after her sixth delivery. She was treated with milk from a castrated goat, with marked benefit, but this improvement was temporary, the symptoms returning after several weeks. The **ovaries** were then **removed**, and a complete cure followed. Stern (Zeit. f. Geburtsh. u. Gynäk., Bd. lxxviii, Nu. 1, 1911).

When removal of the ovaries and uterus cannot be carried out, pregnancy should be avoided, since child-bearing tends greatly to aggravate the disease. In non-puerperal osteomalacia considerable improvement has resulted from **epinephrin** injections.

In addition to the old palliative methods, by means of **baths**, **iron**, **iodides**, etc., we now have the **phosphorus** treatment and the **removal of the ovaries** or even **Porro's operation**. The operative treatment of osteomalacia is as yet not sufficiently developed to allow definite conclusions. Phosphorus is undoubtedly of great value in the treatment of the disease. The operation of choice is **oöphorectomy**. It was discovered

accidentally that the removal of the ovaries produces a marked and rapid improvement in all the symptoms of osteomalacia. The removal of these organs, according to Fehling, induces a set of inverse changes to those which characterize osteomalacia. Curatulo and Jarulli conclude from their study of the subject that the ovaries must secrete some substance which favors the oxidation of organic phosphorus compounds in the body. Bernstein (Roussky Vratch, Sept. 1, 1907).

Case of non-puerperal osteomalacia in a woman of 36. The first symptoms had been observed at the age of 16 after a nervous shock, and were ascribed to a nervous origin until the girl became quite crippled with several spontaneous fractures. Immobilization for a year and a half induced some improvement, but two years later nervous stress and overwork were followed by recurrence and exaggeration of the symptoms of osteomalacia. After two years in bed and failure of all other measures, **suprarenal extract** was given according to Bossi's technique. By the thirtieth injection great improvement was manifest, and in time the entire syndrome was arrested, the bones were apparently restored to approximately normal, all pains ceased, and almost complete functional capacity was restored. From eight to ten injections were made each month, in single doses of 1 c.c. Not a trace of injury from the suprarenal treatment has been discovered in this case. The author is inclined to ascribe its effect to an influence arresting the decalcification of the bones which he regards as the essential process in osteomalacia, both this and rachitis representing practically the same process, differing only in the age at which it occurs. L. Bernard (Presse méd., Nov. 20, 1909).

Case of osteomalacia in which injections of **adrenalin** cured the patient in a short time. From 0.25 to 0.6 c.c. (4 to 10 minims) of the commercial 1:1000 solution was injected

daily. After a total dose of 3.95 c.c. (64 minims) the patient could sit up in bed and even walk short distances, though formerly she was bedridden and the slightest motion caused intense pain. The injections were continued until the patient had received, all in all, 5.5 c.c. (90 minims). She is now completely restored to health. No after-effects were observed except a transient tremor and palpitation of the heart after the larger doses. No other drugs were given except **phosphorus** in **codliver oil** after convalescence. Kownatzki (Münch. med. Woch., July 19, 1910).

Among the less effective—though valuable—methods are long-continued **warm baths**, **salt baths**, **bone-marrow**, and **chloroform**,—though the last has hardly been sufficiently tried to merit confidence.

FRAGILITAS OSSIUM.

The term "fragilitas ossium" is attributed to abnormal brittleness of the bones, due mainly to rarefaction, and predisposing the sufferer to fractures under the influence of slight traumatism, falls, and occasionally without assignable cause. Successive fractures of many bones may thus occur; but, rapid recovery ensuing, the only result is gradually increasing deformity of the patient as a whole and the gradual loss of ambulatory powers.

Multiple fractures may occur during intra-uterine life or in infancy. Nothing is known as to the etiology of the condition, except that there is a strong element of heredity. The number of fractures which may occur in one subject is surprising; in one case 113 were counted. In newborn children with the disease there is generally a combination of old fractures, united and partly united, and of loose recent fractures. Where fractures occur after birth, union is generally good and rapid. The long

bones are the ones chiefly broken, and the thigh most often. The shoulder-blades, skull, pelvis, and spinal column are apparently exempt. Lovett and Nichols (Brit. Med. Jour., Oct. 13, 1906).

Case in which the Roentgen rays showed that 18 fractures had occurred in the course of two years. The patient was a girl of 6 whose older sister displayed the same tendency to abnormal fragility of the bones. The fractures occurred symmetrically. Matsuoka (Deut. Zeit. f. Chir., April, 1909).

Case of fragilitas ossium in a man aged 67. On rising from his chair at the dinner table, the patient was seized with sudden pain in the leg between the knee and hip; the family physician diagnosed fracture at about the junction of the middle and upper third of the left femur. Two months later, while lying quietly on his back in bed, the man was again seized with violent pain accompanying fracture of the opposite limb at about the same location, due to muscular contraction exerting its influence on bone unduly brittle; this fracture, also, was treated in splints with extension, but without the slightest union whatever. It was not until the second fracture had occurred that it was possible to diagnose the condition as fragilitas ossium. Thomas (Texas State Jour. Med., Jan., 1910).

Blue sclerotics as a sign of brittle bones were noted by the writer in 3 cases. Of 13 individuals in the patient's family who had blue sclerotics, 9 gave a history of having had fractures; in 7 these were multiple. In not a single member of the family in which the sclerotics were normal was there a history of fracture. Blue sclerotics, as Buchanan has shown, indicate a deficiency of fibrous tissue in the cornea. H. Burrows (Brit. Med. Jour., July 1, 1911).

ETIOLOGY.—In the majority of cases fragilitas ossium is an inherited dyscrasia the origin of which is still unknown. It is at times associated with

malignant growths, syphilis, rickets, general paralysis, locomotor ataxia, and after injuries involving lowered nutrition of the bony structures through long confinement in bed.

TREATMENT.—Once recognized, prophylactic measures calculated to avoid traumatism and other fracture-causing factors are alone indicated.

In two children one had had 6 fractures and one 7 as a result of slight falls; the bone healed readily and rapidly, with perfect consolidation. In 2 other cases, sisters, about 20 years old, 1 had fractured her leg or arm 10 times between the ages of 5 and 16, the other 11 times before she was 12. These two patients seem to have outgrown the tendency to fractures. They took **calcium phosphate** and **codliver oil** systematically, with special regard to hygiene, and are now apparently in good health. Broca (*Revue de chir.*, vol. xxv, No. 12, 1906).

BONE TUBERCULOSIS.

This name is applied to a chronic tuberculous inflammation of the osseous structures, which may be diffuse or local, superficial or deep. Its specific character is due to the tubercle bacillus. It attacks cancellous bony tissue, the compact usually remaining immune. Thus, when the vertebræ are attacked it is the bodies that are involved, not the laminæ or various processes. Though injury often plays a conspicuous part in its commencement, it is only a contributory factor which provides a suitable nidus or soil in which the tubercle bacillus develops and produces its destructive effects. It is a curious fact that the affection does not appear to start from severe injuries, but from slight ones that cause but little disability at the time of their reception.

SYMPTOMS.—The onset of bone tuberculosis is often extremely insidious, and it may be only after considerable time that the symptoms become at all marked. For this reason early diagnosis of the disease is often difficult. Pain in the affected region, stiffness of the overlying muscles and of the nearest joint, localized tenderness to pressure, and slight increase of local temperature constitute the first series of symptoms observed. The pain is deep-seated, but not sharp; the tissues may feel boggy and are sometimes slightly tumefied, owing to interference with the circulation, as indicated by the enlargement of superficial veins occasionally observed. As long as the inflammatory process is in its incipency, the general health does not suffer. As soon as the bone-tissues begin to disintegrate, however, and pus and tuberculous deposits are formed, and caseation occurs, the local manifestations become decidedly more marked and general symptoms appear and slowly increase: The pain is much greater; pus-channels and fistulæ are formed. When the purulent products are evacuated through the latter, however, the general health may become improved. The fact that the disease may be arrested by removing the foci of infection indicates the pathogenic influence of the local process upon the general organism. The vertebræ, the upper end of the femur, the bones of the hands and feet, and the elbows are the regions most frequently involved. Under **SPINE, DISEASES OF; HIP-JOINT DISEASE, and JOINTS, DISEASES OF**, this important subject is fully treated. The *spina ventosa* of the fingers is a tuberculous disorder.

Study of the records of 22,233 cases of tuberculous bone and joint disease. In 39.1 per cent. the localization was in the spine; in 31.4 per cent. in the hip, and the remaining 29.5 per cent. was divided among the knee, ankle, elbow, wrist, and shoulder in the order named, the knee being involved in 1827 cases and the ankle in 919 cases. Terry and Allison (*Amer. Jour. of Orthop. Surg.*, April, 1907).

In some cases the characteristic symptoms are totally absent, even though the disease is steadily advancing; indeed, months often elapse before the tumefaction is sufficiently large to attract attention.

Tuberculous foci in bones, when no sequestra are formed, may heal spontaneously, but in the presence of such the parts never undergo resolution. Of 314 cases studied by Riedel nearly 46 per cent. were devoid of sequestra. These may be discovered by means of the X-ray or a probe through a fistulous opening. The extent and origin of these tuberculous sinuses can be well determined by injecting them with bismuth subnitrate suspended in vaselin, as suggested by E. G. Beck, and then having a radiograph taken. The injected bismuth shows a very distinct shadow following the course of the sinus. The prognosis depends upon the ease with which operative proceedings can be resorted to and the general care which can be given the patient.

DIAGNOSIS.—The slight general manifestations, especially the unimportant temperature changes; the local tenderness and enlargement, which in the case of fingers is sometimes considerable before actual suffering is induced; coupled with the general appearance of the patient and a family history of tuberculosis,

usually facilitate recognition of the true nature of the affection. The use of Koch's tuberculin for diagnostic purposes by injection has been in the past limited, but more modern methods have made its use safer, and it is especially valuable in doubtful cases. The use of the Calmette method of dropping a prepared solution in the eye is not so desirable, however, as that of von Pirquet, who uses it by vaccination, or that of Moro, who rubs it into the skin. Both of these latter are fairly reliable and satisfactory and not at all dangerous.

In a research by the Local Government Board, London, bacterial reports were made on 116 cases of children suffering from tuberculous bone or joint diseases. The final results of the investigation were as follows: Local reactions to inoculations of both human and bovine tuberculin were invariably present in all patients from whose pus tubercle bacilli had been isolated. Yet the degree of reaction varied within wide limits: Weakly and cachectic patients usually reacted feebly, quite irrespective of differences in the severity of their local lesions; strong and vigorous patients exhibited wide differences in the degree of their reactions, irrespective of differences in the extent or the severity of their local lesions. The quantitative von Pirquet test was not found to be of value in forming an estimate of the severity of the infection, and was of little prognostic value. It was impossible to differentiate the type of tubercle bacillus with which the patient was attacked by the nature of the reaction to the tuberculin employed. H. J. Gauvain (*Lancet*, Oct. 6, 1917).

ETIOLOGY AND PATHOLOGY.

—Heredity, formerly considered to be an extremely important feature of these cases, is now considered to be much less of a causative factor than

is the environment of the patient, although it is true that a tuberculous family history is common. While in some cases of bone tuberculosis the lungs are primarily affected, in by far the majority the infection is probably derived primarily through other portions of the respiratory or alimentary tract, especially the tonsils, nose, throat, intestines, bronchial glands, etc. Tuberculous foci may form in any part of the bone, but particularly in the epiphyses or the spongy portion of the shaft near the epiphysal cartilage. At first limited to the size of a pea, perhaps, it gradually enlarges; surrounding foci are then formed, which coalesce. Several general foci of infection may thus be formed, all containing the bacillus of tuberculosis. The detritus may become transformed into a cheesy or liquid mass; if this does not occur, a sequestrum is formed, which sooner or later becomes free in the cavity, surrounded by caseous pus. Nature tries to remedy the defect by inclosing the cavity in sclerotic bone-tissue, and an ivory-like envelope may thus be formed around the tuberculous cavity. In other cases a limiting pyogenic membrane is generated. Fistulous tracts are developed from these cavities, the pus breaking its way outwardly.

In the tuberculosis dispensary at Naples tuberculosis of the bones often developed in persons with inherited syphilis. This was shown by a study of 70 children from 2 to 13 years old with Pott's disease or other tuberculous affection of bones or joints. In 72.3 per cent., inherited syphilis was beyond question. Treatment for syphilis, in addition to the measures addressed to the tuberculosis, proved quite encouraging. G. Caronia (*Pediatrics*, Dec., 1917).

TREATMENT. — In the early stages symptomatic treatment is indicated, the limb being **immobilized** in such a manner, however, as not to interfere with **outdoor exercise** whenever possible. Indeed, **fresh air** is an important therapeutic factor in all these cases, as is also **nutritious food** and other means calculated to strengthen the patient's general powers.

The **seashore**, the **mountains**, and **pine forests** are remarkably beneficial—as instanced by Arcachon, in France. It is generally recognized that a course of hygienic treatment, such as sleeping out of doors and **extra feeding**, which has been found of such benefit in pulmonary tuberculosis, is likewise of the greatest value in tuberculous affections of the bones. The most persistent efforts should be made to have these hygienic measures carried out because without them in many cases all other therapeutic procedures will be futile.

As urged by De Forest Willard **sunlight** and **fresh air**, with **fixation of the part**, is the best treatment for tuberculosis of hard tissues. Treatment by tent life is successful both in winter and in summer. **Concentration of the sun's rays** is beneficial in the treatment. Both **actinic** and **X-rays** are to be used as adjuncts to other methods, but not as superseding them. **Sea bathing** is also helpful.

A formal **fresh air** and **sunlight treatment**, as elaborated at Berck-Sur-Mer near Boulogne, France; Leysin in Switzerland; Sea Breeze at Coney Island, Southampton, N. Y., and elsewhere, has been the most important advance in bone and joint tuberculosis in a generation. **Sunlight** causes peripheral or local hyperemia and is bactericidal. **Exposure of the skin to air** is in itself beneficial. Rollier begins by gradually exposing the affected area for 5

minutes and increasing the area and the time until a complete exposure is obtained for several hours. Children under the writer's care have been exposed entirely nude for 6 hours a day in the summer with the greatest benefit. Burning of the skin by too energetic treatment may be avoided by using talcum powder freely the first week. H. Ling Taylor (Intern. Abst. of Surg., July, 1915).

The writer applied **heliotherapy** in 16 cases of bone and joint affections. Seven were tuberculous, 4 osteomyelitis, 2 pneumococcic arthritis, 1 peri-arthritis following direct infection of the knee-joint, 1 arthritis deformans, and 1 decubitus. He noticed rapid expulsion of sequestra and a marked and early beneficial effect in severe septic conditions. There is rapid evolution of the tuberculous process, resulting in bony ankylosis in every case. Close attention should be given to **orthopedic measures** for the prevention of the deformity, as in any previous treatment, by using removable apparatus and extension. W. C. Campbell (Amer. Jour. Orthop. Surg., xiv, 191, 1916).

The writer holds that for bone tuberculosis **X-ray** treatment is the best as this alone, without adjuvants, can insure a cure. In case of a fluctuating abscess or large sequestra it may not even be necessary to resort to the bistoury or the curet. Thanks to the X-rays the sequestra are often spontaneously eliminated. **Heliotherapy** and **sea air** are always useful adjuvants, but they are not absolutely indispensable unless there are multiple tuberculous foci. Weil (Paris méd., June 2, 1917).

Exposure to the **sun's rays** has a speedy beneficial effect, the latter being emphasized by the retrogression which occurs when the treatment is interrupted. It is not certain that the ultra-violet rays are the only active part of the sun's rays inasmuch as the therapeutic effect is not obtained with artificial sources of ultra-violet rays. Freiberg (Amer. Jour. Orthop. Surg., Sept., 1917).

In surgical tuberculosis the writer attempts to excite the circulation locally by the use of **heat**, thus provoking more active vascularization. For this purpose a flexible thermophile or heat conducting tissue is used, which adapts itself closely to the shape of any area of the body measuring up to thirty by forty centimeters, and is applied over a few layers of gauze. Upon heating with the electric current the temperature rises in a few minutes to 50°, 60°, 70°, or even 80° C. A thermometer passed permits watching the temperature attained. The heat is applied daily or on alternate days for 10 to 20 minutes, according to the persistency of the vascular reaction provoked. Above 50° C. the virulence of the tubercle bacillus begins to be impaired, and phagocytosis, favored by the increase of local circulation, becomes correspondingly more effective. For bony and lymphatic involvements, the optimum temperature is 50° to 70°. Into the depths of sinuses or at the surface of open lesions, **powdered metallic copper** in small amount is placed every two to four days. The resulting nascent copper chloride exerts a distinct antiseptic effect, and progressive improvement in the local condition is noted. Luton, a few years ago, maintained that **copper acetophosphate** would cure tuberculosis. In the writer's hands the treatment proved especially effectual in tuberculous glandular involvements. For small areas, the electrically heated tissue was sometimes replaced by small sacs of sand at 50° to 70° C., with satisfactory results. Berthier (Jour. de méd. de Paris, Jan., 1918).

Reports of results obtained at the Ilbarritz Hospital for surgical tuberculosis cases, near Biarritz, on the southwestern coast of France. All bone and joint cases have a plaster apparatus in which windows are cut to expose the diseased area to the **sun's rays**. Punctures, injections, and orthopedic appliances are used

as indicated. Although only 6 months had passed since the opening of the hospital, 24 patients had already been evacuated completely cured out of a total of 180 cases received and 34 others were on the road to good recovery. The latter included 13 cases of Pott's abscess. Peyret and Fournier (*Jour. de méd. de Bordeaux*, lxxxix, 89, 1918).

Local treatment is sometimes very effective. One of these consists of **injections** with a syringe into diseased areas of a 10 per cent. solution of **iodoform in oil**, sterilized by heating to the boiling point. But each agent should be sterilized separately; in this manner the toxic effects of the iodoform are avoided. **Betanaphthol**, 1 part; **camphor**, 3 parts; when finely powdered and mixed, form an oily liquid which may be dissolved in ether, chloroform, and fats; Reboul has used this remedy in various strengths in tuberculous cavities, with signal success. Some surgeons favor **ignipuncture** with galvanocautery or thermocautery; especially effective is the filling of the cavities with the iodoform and wax **paste** of **Mosetig-Moorhof** or with subnitrate of **bismuth paste**, as suggested by E. G. Beck and already alluded to.

The **Mosetig-Moorhof iodoform bone filling method** is easily applied and most satisfactory in cases of bone cavities which are sterile or nearly so at the time of operation. Thus, in cases of bone cysts or early and localized tuberculous disease, primary healing usually may be expected; and even in cases of bone abscess with attenuated infection, healing usually will occur without further interference, though a sinus may persist for some months. Ashurst (*Annals of Surg.*, Feb., 1917).

The method proposed by Durante, which Mortari has used on a large scale with satisfactory results, consists of in-

jections of **iodine** and **potassium iodide solutions** under the skin, into the muscles, and into the cavities and sinuses. The action of **iodoform emulsion**, which has so long been used for this purpose, is due to the liberation of iodine. But this takes place very slowly in the tissues at the normal temperature. The iodine-potassium-iodide solution, however, is much more prompt and efficient. He employs the following formula:—

R Iodine 4½ grs. (0.3 Gm.).
Potassium iodide . 45 grs. (3 Gm.).
Glycerin,
Distilled water, of
each 750 mins. (47 c.c.).

M.

Operative measures are of great value. If the local condition is acute, the active symptoms may often be made to subside at once by drilling a half-dozen holes 3 mm. in diameter into the part for a local depleting effect and then encasing the limb in **plaster of Paris**, thus keeping it at absolute rest. The affected area of bone may also be removed by the gouge and the use of the curette. This must be done thoroughly, however, every vestige of diseased bone or its contents being carefully removed. One small focus may serve for the development anew of all the symptoms. The same radical measures should be used in adjoining cavities or surfaces; no tuberculous center should remain. The cavity should then be filled with **iodoform** or **bismuth paste**. After all operative procedures the same scrupulous care must be taken to insure absolute quiet of the part by means of **fixation splints**, usually of plaster of Paris, as is used when no operative interference has been undertaken. For the treatment of the ulcerative conditions of the skin and superficial parts which so often complicate tuberculous affec-

tions and delay wound healing there is nothing so efficient as repeatedly touching up the ulcerated surface with the **solid stick** of nitrate of silver every two or three days.

Amputation used to be frequently resorted to in severe and obstinate cases; modern antiseptic methods have modified this tendency, and very few cases nowadays cannot be satisfactorily treated. Recently the use of **tuberculin** and **vaccines** controlled and guided by the opsonic index according to the method of Wright has been tried by various observers. The results have apparently been encouraging, but have not as yet been conclusive as to its value. The practical difficulties in the way of properly carrying out the method have greatly interfered with its receiving a proper and extensive test.

Inoculations by **bacterial vaccines** and **tuberculins**, either alternately or separately, depending upon the condition of the patient, furnish a valuable accessory therapeutic measure in the routine antituberculous hygienic and surgical treatment of mixed suppurative bone and joint disease. Bacterial vaccines, especially tuberculins, are more potent agents for evil than for good, unless competently administered. Carefully employed, cases do better with than without bacterial vaccines, their detention in the hospital is materially shortened, and complications, if they occur, are fewer and less severe. The therapy is superfluous in mild cases where simple operation and time will effect cure; nor is it applicable to neglected cases with prolonged suppuration, characterized by bacteremia, grave sapremia, and amyloid disease. So long as the temperature fluctuates above 100°, **autogenous vaccines**, obtained by culturing and reculturing the suppuration found to contain variable bacteria from time to time, are administered. Tuberculin inoc-

ulations are begun when the temperature falls to 100° or preferably lower.

Better results have attended the process of active immunization where, just as in tuberculin therapy pure and simple, the treatment has been commenced with relatively small bacterial inoculations, progressively increased to the therapeutic limit, rather than by recourse to large dosage, thereby establishing immunity in the former case and in the latter avoiding anaphylaxis. Willard and Thomas (*Annals of Surgery*, June, 1910).

Under modern **tuberculin** treatment the author's recoveries in bone and joint tuberculosis have averaged 68 per cent. against 34 per cent. when treated without tuberculin. In addition, the period of treatment of recovered cases averaged only 11½ months, as against 5¼ years without tuberculin. Tuberculin checks the local process, the individual also regaining and maintaining strength not attained by treatment alone on general hygienic and orthopedic lines. Twinch (*Amer. Jour. Orthop. Surg.*, Sept., 1918).

After 73 Cesarean sections in as many cases of osteomalacia with a mortality of 23.3 per cent., the writer states that such patients are poor subjects for operation, and better results may be expected in other maternity cases. Neve (*Pract.*, Dec., 1919).

Three years after the onset of the disease in a secundipara, aged 38, the writer **removed the ovaries**. Twelve months later the patient was greatly improved in all respects. Hellier (*Brit. Med. Jour.*, Oct. 16, 1920).

Marmoreck's serum, so highly praised by Hoffa, has not as yet proved to be of any decided value.

Bier's hyperemia method has given encouraging results. According to Deutschländer, it should be applied daily one or two hours, causing the region to become red—a rather painful procedure which must be continued several weeks. The other measures recommended above being

comparatively painless, they should be given the preference before resorting to hyperemia.

Good results have been obtained from **X-ray** treatment; this method presents the advantage of not preventing the simultaneous use of other measures.

TUMORS.—Osseous tumors may be either malignant or benign. The more common of the former are various forms of sarcoma, according to the tissues from which they originate. Thus, a fasciculated sarcoma develops from the periosteum while the myeloid sarcoma develops in the endosteum expanding the bone proper. Fibrosarcoma and myxosarcoma are not uncommon. Bones may also become the seat of secondary cancerous or sarcomatous deposits originating from foci elsewhere in the body.

Persistent severe and localized pain in a long bone, according to W. B. Coley (*Annals of Surg.*, Nov., 1914) should lead to suspicion of malignant growth. Early sarcoma rarely involves joints, different from tuberculosis. Exostoses are slower in growth; painless, harder, and more uniform. Myelomata show a globular expansion of a limited portion of bone without deposition of new bone on the outside and without tendency to involvement of the shaft. They usually grow slowly, but occasionally very rapidly, many even metastasizing. The X-ray findings must be carefully interpreted. In periosteal sarcoma there is a tendency to form spicules at right angles to the shaft. In myositis ossificans there is usually a sharply defined periosteal line. In case of doubt, repeated measurements and X-ray examinations at 2-week intervals are of great value. Exploratory incision is permissible in doubtful selected cases, but not as a routine measure.

The pioneer in the local removal of bone sarcomata when the tumor is encapsulated and not of the most malignant character was J. B. Murphy. Local operation gives the patient as good a chance as an amputation in these cases, and if followed by a graft leaves a useful limb. Re-

currence, when it takes place, is distal, not local. It is usually possible to get the consent of the patient at an early date for an **excision**; hence the chances of metastasis are less, while consent for amputation is usually only given as a last resort. A graft is apparently not necessary in removal of the upper part of the fibula. P. J. Byrne (*Pract.*, Feb., 1917).

Among the benign growths may be mentioned osteoma, chondroma, cysts due to hydatids and actinomycosis "the lumpy jaw" of cattle. Another form is the dentigerous cyst, which occurs in the maxillary bones. Bones are often the seat of gummata.

Surgical treatment of an osteoma varies in its results according to the stage of the growth. Young osteomas show a central bony mass and a peripheral shell of varying thickness composed of young cells gradually undergoing osseous transformation. This process may occupy months or years, and the only means of ascertaining the precise condition of the growth is the use of the X-rays. An osteoma may be classed as young as long as its X-ray shadow is smaller than its clinical size. Any young osteoma taken out surgically without complete removal of its shell, the limits and thickness of which cannot be ascertained, will inevitably recur. Adult osteomas, which have stopped developing and have no such shell, yield an X-ray shadow equal to their clinical size and will not recur upon surgical removal. Artificial aging of osteomas by means of the **X-rays** was attempted by the authors in 2 cases, with unexpectedly good results. Chevrier and Bonniot (*Presse méd.*, Oct. 25, 1917).

The origin of osseous cysts may be traced to a variety of causes: past inflammation, softening tumors, such as chondromata and sarcomata, and to ossifying diseases such as osteoporosis, osteomalacia or ostitis fibrosa. There are also cysts the walls of which often contain a giant cell

tumor rich in cells of sarcoma-like structure, even when the disease could not possibly be regarded as a malignant growth. Osteitis fibrosa occurs chiefly in the young adult; trauma is the usual etiologic factor. Slowly the bone swells, causing rheumatic pains; fibrosis of the medullary tissue follows, with rarefying osteitis and cyst formation. The X-ray is of great help frequently. A sarcoma usually shows periosteal changes. The treatment is surgical, but conservative. When there is a cyst, with serum-like contents, remove the serum, scrape the walls, and push in the shell. Preserve the periosteum as this will form callus to fill up the cavity. During the scraping, profuse bleeding may occur, so an Esmarch band is used. If the cyst is so large that removal causes the bone to break, bone grafting or ivory stick may be resorted to. Microscopic examination of the excised tissue does not always determine the diagnosis. E. Platou (*Annals of Surg.*, Mar., 1918).

Multiple fibrocystic and cystic lesions in bone, which are non-neoplastic, are due to some general systemic disturbance, viz., metabolic processes, syphilis, tuberculosis, other bacterial infections, parasites, hemophilia. Metabolic processes are due to interference with the functions of the endocrine glands. In this subclass are included osteitis fibrosa cystica and osteitis deformans. The congenital more often than the acquired form of syphilis frequently shows localized cystic or fibrocystic areas in the cancellous bone.

A second group includes solitary cystic and fibrocystic bone lesions. Seventy-five per cent. are due to bone trauma. They are usually painless. In pathological fracture, X-ray of the entire skeleton will often reveal fibrocystic lesions in other bones. Treatment of the solitary lesion consists of thorough curetting and swabbing with tincture of iodine. All cavities larger than a pigeon's egg may be filled with shavings taken

from adjacent bone, to shorten the process of repair. G. Barrie (*Annals of Surg.*, lxvii, 354, 1918).

Hemorrhagic osteomyelitis should be differentiated from the true sarcoma found in bone. Giant cells, of the type commonly found in some of the low-grade malignant sarcomas, are also present in most of the non-infective low-grade inflammatory processes in bone. In true sarcoma, regardless of the degree of malignancy, there is never a resting stage; the increase in size of the neoplasm is progressive and constant. In hemorrhagic osteomyelitis, increased bone destruction, following initial injury, is due to nutritional inhibition and necrosis of bony structure resulting from pressure of the proliferative granulation tissues. Hand in hand with destruction, efforts at regeneration and rebuilding of normal structure go on, evidence of which is seen in the formation of primary elemental granulation tissue. Barrie (*Amer. Jour. of Oroph. Surg.*, Nov., 1918).

GWILYM G. DAVIS,
Philadelphia.

BONE-MARROW. See ANIMAL EXTRACTS.

BORACIC ACID. See BORIC ACID.

BORAX. See BORIC ACID.

BORIC ACID.—Boric or boracic acid [H_3BO_3] appears in the form of white, translucent or lustrous scales, or as a powder, and is usually prepared by adding hydrochloric acid to a hot solution of borax (sodium borate). It has a faintly bitter taste, and shows a feeble acid reaction with litmus. It is soluble in 18 to 26 parts of water at 25° C., in 3 parts of boiling water, in 15 parts of cold alcohol, and in 4½ parts of glycerin; it also dissolves in chloroform and in oils. Addition of hydrochloric acid decreases the solubility of boric acid in water.

Heated to 100° C., boric acid loses water, passing into metaboric acid [HBO_2], which becomes slowly volatilized. On boiling a solution of boric acid, it escapes, with the steam. An alcoholic solution of the acid burns with a green flame—a fact which affords a ready means for detecting it.

PREPARATIONS AND DOSE.—

Besides the acid itself, *acidum boricum*, the dose of which is from 5 to 15 grains (0.33 to 1 Gm.), and which is soluble in 18 to 26 parts of cold water, as stated above, the following are official preparations:—

The *glyceritum boroglycerini* (the glycerite of boroglycerin), composed of boric acid 310 parts, glycerin 690 parts, employed externally.

The *liquor antisepticus* (antiseptic solution), containing 2 per cent. of boric acid, with mild antiseptics and aromatics, such as benzoic acid, thymol, eucalyptol, and oils of peppermint, wintergreen, and thyme.

The *unguentum acidi borici* (ointment of boric acid), an ointment of paraffin and white petrolatum, containing 10 per cent. of boric acid.

The *sodii boras* (sodium borate or borax), colorless or white, crystalline powder, having a sweetish taste, soluble in 16 parts of water, 1 part of glycerin, but not at all in alcohol. Dose, 5 to 20 grains (0.33 to 1.3 Gm.).

INCOMPATIBLES.—Boric acid is incompatible with carbonates and bicarbonates, and the alkaline earthy and metallic bases. Sodium borate is incompatible with the acids and metallic salts, and precipitates cocaine and morphine in solution.

PHYSIOLOGICAL ACTION.—

Boric acid and all its salts are deemed more or less antiseptic, and the for-

mer has attained special repute because of its inexpensiveness, general harmlessness, and supposed unirritating character, virtues which in reality apply only to weak solutions. But purity is always to be carefully considered, both as regards external and internal use. It is not so commonly employed as an internal medicament, perhaps, as the sodium salt, because of its somewhat pungent and acid taste, and partly because it is deemed less convenient to prescribe in aqueous mixtures. In large doses, however, both it and the salts depress the spinal centers, and may produce progressive loss of voluntary and reflex activity without affecting nerve or muscle. Schiff found that boric acid, when locally applied to nerves, caused the part to lose the power of originating, but not of transmitting, impulses; so that, if the galvanic current be applied to the part of the nerve which has been exposed to the drug, no muscular contractions result; but, if the poles be placed above this part, the distal muscles respond at once. Boric acid and, to a less degree, sodium borate retard the diastasic action of the saliva upon starches, while increasing, according to some observers, that of the pancreatic products. This probably applies, however, only to small doses, for it tends, in moderate doses, to delay absorption of both proteins and fats.

In large doses often repeated, boric acid is likely to induce nausea and vomiting, and, if persisted in (or even in large, single doses), to check gastric digestion and give rise to a concatenation of symptoms indicating gastroenteritis by a direct action, as shown below. Both boric acid and sodium borate also tend, in large

doses, to promote contraction of the uterine muscle, and may thus act as an echolic.

Diuresis with increased desire to urinate has been found to follow doses of from 30 to 120 grains (2 to 8 Gm.); the acid is eliminated through the kidneys, causing albuminuria in persons predisposed to it, and also escapes with the perspiration, saliva, and feces. It enhances the elimination of urea, as well as the flow of urine.

POISONING BY BORIC ACID AND SODIUM BORATE.—The symptoms of poisoning are, briefly, a sensation of severe uneasiness in the stomach and intestines, with dryness of the throat, difficulty in swallowing, nausea, vomiting, diarrhea; headache, with dimness of vision, and somnolence, lassitude progressing to intense weakness, leading to collapse and even death.

Case of poisoning in an 8 months' old baby, due to milk given which contained boric acid, 5 grains (0.3 Gm.) to the pint (500 c.c.). The child had been taking from 7.5 to 10 grains (0.5 to 0.65 Gm.) of the preservative daily. A new supply of fresh cow's milk caused the symptoms to cease and within a couple of days the child began to get well, though it was some months before it was normal again. Forsyth (*Lancet*, Oct. 25, 1919).

Though some authors insist that very large doses are necessary to produce dangerous symptoms, this is not supported by general evidence, for it has been known that relatively small doses suffice to induce the above phenomena, and also nephritis. This is especially true of the sodium salt, which is a dangerous remedy as regards most renal disorders, and seems to possess the power of provoking de-

generation where a morbid process has already been set up in the kidneys. Cases have also been reported in which the local application of powdered boric acid produced general toxic symptoms: in one case the skin had a dried, "charred" appearance, and in the other there was collapse; in 2 there was very marked coolness of the vagina, to which it had been applied on a tampon. A bluish-gray line on the gums, as if from lead poisoning, has been observed in a case of epilepsy to which sodium borate had been given. Cases have also been reported as poisoned through the daily application of 30 grains (2 Gm.) of the acid. In one case there were restlessness and a feeling of burning under the whole skin, intense thirst, a temperature of 38.8° C. (101.8° F.), and the body covered with red patches; in another case an eczematous eruption, anorexia, and insomnia appeared. In both cases the untoward symptoms subsided immediately on withdrawing the acid applications. What is said of the acid applies, in a general way, to its salts.

Boric acid and borax do not belong to the class of substances that are inactive and without danger. H. Rost (*Deut. med. Woch.*, Feb. 12, 1903).

Case of fatal boric acid poisoning. The inguinal glands had been excised and the cavity packed with about 6 ounces of boric acid powder. Soon after the operation the man developed the typical signs of boric acid poisoning: profuse vomiting; a papular rash over the face, neck, and chest, and a weak, irregular pulse. The onset was rapid and the fatal issue came on within four days. There was also delirium and slight rise of temperature. C. I. Best (*Jour. Amer. Med. Assoc.*, Sept. 17, 1904).

Case of a 2-year-old child suffering from a burn measuring 12 to 13 cm.

To this, fresh boric acid ointment was applied. Soon there appeared a scarlatiniform rash, petechia, and evident head symptoms. Three days later the child died. The possibility of children having an idiosyncrasy for this drug warns against the danger that may ensue upon its use in burns or in other cases where a raw surface favors absorption of the drug by the patient. Dopfer (*Münch. med. Woch.*; *Der Kinderarzt*, Feb. 2, 1906).

Case of boric acid poisoning from the use of rectal irrigations of boric acid solution in dysentery. There appeared a rash resembling a bromide rash, delirium, and feeble pulse, suddenly and without warning. The eruption persisted after all drugs had been stopped. J. H. Sanders (*Brit. Med. Jour.*, March 16, 1912).

The writer formerly used boracic acid solutions for lavage of the bowels in cases of colitis, but after having seen symptoms arise in at least 3 patients, decided it might not be such a harmless method as one would be inclined to believe. Harley (*Brit. Med. Jour.*, Apr. 13, 1913).

Case of a baby 7 weeks and 6 days old who was given about 3 ounces (90 c.c.) of a saturated solution of boric acid instead of boiled water. It vomited while being nursed, so that this was discontinued, and 3 more ounces of the boric acid solution were given. Copious movements followed, which soon became nothing but clear, jelly-like mucus, and vomiting continued for about 36 hours, gradually decreasing in severity. Two days after the first ingestion there appeared a slight miliary eruption on the neck, chest and back. The disease ran its course rapidly and the peeling was completed in about 10 days. The baby rapidly recovered. P. Wilson (*Wash. Med. Annals*, Nov., 1915).

TOXIC EFFECTS OF BORIC ACID AS A FOOD PRESERVATIVE.—Boric acid plays no part in the vital process; but it destroys life even in weak solutions. Hoffmann

(cited by Franz, *Deut. med. Wochen.*, Bd. xxviii, p. 832, 1902) has shown that fish die within two days in a solution of boric acid as weak as $\frac{1}{4}$ (0.25) of 1 per cent. Not only were severe intestinal disorders produced, but the outer skin was itself inflamed. When the relative sensitiveness of the mucous membrane of the alimentary canal of those infants and individuals who depend solely upon cows' milk for sustenance is taken into account, the judgments of English courts against dealers who had sold milk containing as small proportions of boric acid as $\frac{1}{30}$ and even $\frac{1}{37}$ of 1 per cent. (*Brit. Food Jour.*, vol. x, p. 212, 1908; vol. xi, pp. 10 and 15, 1909) are fully warranted. That such limited adulteration renders milk or cream poisonous is beyond doubt. Fourteen grains (*N. Y. Med. Jour.*, vol. lxxxiii, No. 14, April 7, 1906) in divided doses daily have been found to cause severe gastrointestinal disorders in adults at the end of three days. Now, an average infant 6 months old, fed artificially on cows' milk, consumes 36 ounces a day. With a proportion of $\frac{1}{30}$ of 1 per cent. of boric acid, a pint of such milk would contain $2\frac{1}{2}$ grains (0.16 Gm.). As 36 ounces represent 2 pints and 4 ounces, we have an aggregate of 5.625 grains in the infant's daily food, eight times more than necessary to provoke the toxic phenomena in adults referred to above, since an infant 6 months old requires but one-twentieth of an adult dose (Griffith, *Lectures at the University of Pennsylvania*) to show corresponding effects, i.e., $\frac{1}{10}$ of a grain (0.045 Gm.) in the present connection. An infant brought up on artificial food, especially among the poor and ignorant, is often given,

with the best intentions, practically anything in the farinaceous line, in the form of soup or pap. Such foods are also used extensively, along with milk, for invalids, particularly those suffering from gastric disorders. A prominent authority, Pouchet, of Paris, holds (*Pharmacologie et matière médicale*, p. 805, 1907), with others of equal rank: Halliburton (*Brit. Med. Jour.*, 1900, vol. ii, p. 1), Weitzel (*Arbeiten aus dem Kaiserlichen Gesundheitsamte*, vol. xix, part 1, 1902, p. 126), that even in minute amounts boric acid interferes with digestion by decreasing the strength of the gastric and pancreatic juices, and urged that its use as a preservative be "rigorously proscribed"; he is suggestively sustained by the many cases of infantile diarrhea traced by Tubb-Thomas (*Public Health*, vol. xi, 1898-99, pp. 528-538) to milk containing this preservative, and by the conclusion of Annett (*Lancet*, 1899, vol. ii, pp. 1282-83-85), after a searching inquiry into the subject, that to such preservatives must be mainly ascribed the great infant mortality during the summer months. While the combination of boric acid milk and boric acid crackers will practically insure death for the unfortunate infants whom mercantile methods will have subjected to such a fate, many of those yet safe because pure milk is still within their reach will be doomed, if their auxiliary foods happen to contain boric acid, even in as small a proportion as $\frac{1}{20}$ of 1 per cent.

Worthy of note also in this connection is Förster's remark (*Hyg. Rundschau*, 19, 169-185) that the work of mixing (a difficult task) is usually entrusted to careless and

ignorant hands, and that variations of from 1 to 4 per cent. were to be found in treated foods. What guarantee is there under such conditions that uneven distribution will not greatly increase the danger?

But it is not only in the infant that foods containing boric acid are harmful. It applies particularly also to the multitude of sufferers from disorders of the stomach, intestines, and kidneys, and to the neurasthenic and debilitated.

To quote the words of Medical Officer Hill, of Birmingham (*Public Health*, vol. xi, 1898-99, pp. 528-538), "A number of experiments have been made on men and animals by Mattern, Förster and Schlenker, and Chittenden, with the result that they all found that smaller or larger doses interfered with digestion and nutrition." Comparative trials on himself with cream showed Allan (*Brit. Food Jour.*, vol. x, pp. 151, 1908) that dyspepsia appeared only during the periods when the cream contained boric acid. Its evil effects in moderate doses have also been recorded by Kenwood (*Brit. Food Jour.*, vol. x, p. 97, 1908), Merkel (*Münch. med. Woch.*, vol. 1, p. 1, pp. 100-101, 1903; *Lancet*, March 14, p. 749, 1903), and others—indigestion, headache, flatulence, abdominal pain, and diarrhea, ceasing only when the use of boric acid was discontinued. We need not wonder at these effects, since, as shown by Hoffmann, of Berlin (*Deut. med. Woch.*, Bd. xxviii, S. 832, 1902), strong, fresh-caught frogs "placed in a weak boric acid solution" in such a manner that this solution touches only the lower part of the body will soon develop great blisters in the immersed portion, the "epithelial

layers of the skin being then dissolved off so that large pieces float on the liquid." Even when the solution was but *one-half of one per cent.* ($\frac{5}{10}$ per cent.) the inflammatory process developed, with loss of the same skin tissues on the second day.

This accounts for the most disastrous effect of boric acid: the destruction of the lining epithelium of the intestinal canal, so important in the process of absorption of foodstuffs that its loss means death from starvation.

Thus, Hoffmann (*loc. cit.*) found that dogs whose food contained 2.5 per cent. of boric acid showed, *post mortem*, marked lesions of the stomach and intestines. The epithelium had peeled off in places; there were necrotic areas, while large pieces of mucous membrane had sloughed off. In rabbits a 1 per cent. solution sufficed to raise blisters on the intestinal surface and to cause its lining to be thrown off. Similar experiments by Puppe (*Aertzliche Sachverständigen-Zeitung*, Bd. xiii, S. 313, 1907) in dogs gave similar results, and he compares the action of boric acid to that of corrosive sublimate. But he observed moreover that the decrease of weight in all the animals was, in his own words, "extraordinarily noticeable." In experiments by Pouchet (quoted by Brouardel, *Les Empoisonnements criminels et accidentels*, Paris, 1902, p. 277) the dogs lost one-fifth to one-sixth of their weight. In man 3 grains (0.2 Gm.) of boric acid daily (many adulterated milks contain more than this proportion to the pint) suffice to decrease the weight, as shown by Rost (*Arbeiten aus dem Kaiserlichen Gesundheitsamte*, Bd. x, part 1, 1902), who also

attributes the rapid emaciation to loss of power by the intestine to assimilate food. Kister's (*Zeitsch. f. Hygiene*, Bd. xxxvii, S. 225, 1901) experimental kittens soon died with what he terms "intensified inanition" precisely as do infants exposed to the same corrosive action of boric acid introduced in what is supposed by their parents to represent their *pabulum vite*, milk.

"Consider," writes Rubner (*Arbeiten aus dem Kaiserlichen Gesundheitsamte*, vol. xix, p. 1, 88, 1902), "the serious consequences which, for instance, may occur in the nourishment of children, in that of old and enfeebled persons, convalescents, in which cases the preservation of life itself depends on carefully regulated food!"

An important feature of the action of corrosive substances such as boric acid is the decrease of resistance to disease their use entails. Boric acid is particularly harmful in this connection, as shown by Bernstein (*Brit. Med. Jour.*, April 16, p. 928, 1910), because it is endowed with a selective action, not for the harmful and ubiquitous intestinal germ, the *Bacillus coli communis*, but for germs of the proteus group and other harmless saprophytes. In other words, it kills harmless bacteria just as it does the lining epithelium of the intestine, thus leaving in the latter a breach, or, indeed, numerous breaches, through which harmful bacteria can penetrate into the blood and neighboring tissues and infect them.

As a preservative agent for meat boric acid has also been found by Bernstein (*Brit. Med. Jour.*, April 16, 1910) to prevent decomposition in so far as the sense of smell is concerned. If putrefaction has begun, the fact

that it inhibits the growth of yeasts and organisms of the *proteus* group and other harmless saphrophytes, but not the organisms of the coli group, makes it possible with the aid of boric acid to use stale meat for the making of sausage, and even meat that has already started decomposing. If, then, to such meats Gaertner's bacillus has obtained access, it will have had several days at least in which to grow, and, what is important, unhindered by the protective saphrophytes. Such meat is therefore pathogenic as a food.

If we now inquire into the harm that boric acid can do in the intestinal canal by sparing the *Bacillus coli* and opening avenues for it into the blood, we shall find that boric acid renders those who use it vulnerable to many diseases besides infantile diarrhea. Even the most conservative bacteriologists sustain Kramer (Jour. Exp. Med., p. 319, 1907) in the discovery that the colon bacillus takes an important part in the formation of gall-stones. Rostocki (Deut. med. Woch., p. 235, 1898) and others have found that 80 per cent. of all diseases of the urinary tract, and particularly of the bladder, were caused by the same bacillus. It has also been recognized by many as an active agent in certain ulcerative processes, especially upon abraded surfaces. Important in this connection is the fact that the *Bacillus coli* is ever present in the intestine, and if we recall that, besides destroying the epithelial lining of the intestine, boric acid also causes necrosis and enlargement of the lymphatic glands, as shown by Puppe (Aertzliche Sachverständigen-Zeitung, Bd. xiii, S. 309, 1907), we can understand why Richard Jones

(quoted by Harrison, Lancet, Sept. 22, p. 787, 1906) connected the marked increase (133 to 305 per million) of deaths in Great Britain during 1885-1904 from enteritis, appendicitis, and perityphlitis with food preservatives, including boric acid, since each of these diseases presents, as a prominent feature of its pathology, ulceration of the intestinal lymphatic glands.

Typhoid fever is due to a specific bacterium, that of Eberth, while the ulcerative lesions of the intestine include the lymph-follicles and glands. But the specific germ does not alone work havoc in these cases; the lesions may also be provoked by other bacteria, including the *Bacillus coli communis*. Indeed, there is good ground for the belief that these organisms are able alone to cause typhoid fever; Smith and Tennant, in the Belfast epidemic, for example, failed to find typhoid bacilli in the causative water supply, but were able to isolate the *Bacillus coli*. The intestinal canal being constantly the host of a multitude of these germs, any substance capable of injuring the lymphatic glands affords an entrance to the bacillus with ulceration and typhoid symptoms at least as a result. We have seen just such an agent in boric acid.

Appendicitis is another disorder worth considering in this connection. As Reginald Harrison, of London (Lancet, Sept. 22, p. 787, 1906), says, adding testimony of his own: "It has been stated with some authority that the frequency of appendicitis has been considerably added to in recent years by the large use of boric acid and other chemicals as food preservatives." Injury of the lymphatic

glands by these agents also explains the causative rôle boric acid can play in this disease. Sajous (*Internal Secretions*, vol. i, p. 325, 1903) pointed out in 1903 that the vermiform appendix was not the useless organ it was generally supposed to be, and that its purpose was to supply, through the lymph-follicles it contains, phagocytes and antitoxic substances calculated to destroy bacteria and their toxins in the cecum, where, as the end of the small intestine, its content has undergone advanced putrefaction. This view has been confirmed by E. M. Corner, of London (*Annals of Surgery*, p. 513, Oct., 1910), who, referring to the opinions of Keetley and Macewen, that it was an actively useful organ, states that the vermiform appendix is "a specialized part of the alimentary canal, nature having made use of a disappearing structure and endowed it with a secondary function, by giving it lymphoid tissue to protect the body against the micro-organisms of the ileocecal region." As it is this lymphoid tissue in the intestine proper that boric acid, as shown by Puppe (*Aertzliche Sachverständigen - Zeitung*, Bd. xiii, S. 309, 1907), destroys, while, as we have seen, it also paralyzes the germ-destroying cells, the phagocytes, it becomes evident that it renders the appendix itself vulnerable to the action of the local bacteria, *i.e.*, to that inflammatory and ulcerative process recognized as appendicitis.

Bright's disease, including the various kidney disorders grouped under this head, is, of all conditions, one of the most seriously aggravated by small as well as large quantities of boric acid. "What constitutes danger," writes Brouardel, of Paris,

referring to food preservatives in general, "is the daily ingestion of small amounts: by accumulation these small amounts may become a dangerous amount; in the elimination of them the organs charged with this function become irritated." This is precisely the characteristic action of boric acid upon the kidneys. As shown by Rost (*Archives Intern. de Pharmacodynamie et de Thérapie*, 1905, vol. xv, pp. 290-331) and others, only minute quantities of this corrosive salt leave the body by the intestine or with the sputum, milk, or sweat. Not only are the kidneys practically the sole organs through which it is eliminated, but they excrete it slowly, so that it requires from five to eighteen days to eliminate even a moderate dose. Used continuously as it is in food, boric acid accumulates in the blood, subjecting the kidneys to constant irritation. Gaucher (quoted by Catrin, *Bull. et mém. de la Soc. des hôpitaux de Paris*, 1896, ser. 3, vol. xiii, p. 610) has shown that it caused inflammation of these organs, *i.e.*, nephritis, in guinea-pigs; Kister (*Zeitsch. f. Hygiene*, Bd. xxxvii, S. 225, 1901) found albumin in the urine of human experimental subjects on the fourth to the tenth day of food containing boric acid; Harrington (*Amer. Jour. Med. Sci.*, Sept., pp. 1-9, 1904) observed kidney lesions in cats fed in the same way, cats fed with the same food, but without boric acid, showing perfectly healthy kidneys.

The salient feature in this connection is not so much the production of Bright's disease as it is the fact that milk diet and farinaceous foods are used extensively in this disease. In the light of the above facts, what may

we expect from such foods, even though they contain but a small proportion of boric acid? The answer needs hardly to be emphasized.

Finally, we must not overlook the fact that boric acid is an active poison a single large dose of which may kill in thirty-six hours where kidney lesions are present, as in Schwyzer's case (N. Y. Med. Woch., No. 8, 1895). Many instances of poisoning have been reported not only in cases in which boric acid had been ingested, but also where it had been used locally, enough having been absorbed to cause death. Nor does this apply solely to large doses. Five- and three-grain doses—much less than there is in a quart of the average "preserved" milk—have produced, after a few days, violent toxic phenomena. To ascribe these effects to "idiosyncrasy," "special sensitiveness," and the like means nothing in view of the facts adduced herein concerning the cumulative action of foods containing but $\frac{1}{20}$ or $\frac{1}{30}$ of 1 per cent. of boric acid. Even if such excuses had any weight at all, such hypersensitiveness should preclude its use. But we have, besides, the plea of the sick, the convalescent, the cripple, the infant—of the multitude of innocent victims—to take into account, and all impose the duty formulated by Pouchet (Recueil des Travaux du Comité Consultatif d'Hygiène, 1891, vol. xxi, p. 699) to the Committee of Public Health of France over twenty years ago, and acted upon at once, to the effect that *the use of borax or of boric acid should not be authorized in foodstuffs*.

THERAPEUTICS.—Boric Acid.—

The germicidal value of boric acid is limited, since it does not destroy

pathogenic bacteria. Yet, it presents the advantage, in 4 per cent. solution, of inhibiting their growth. Hence its wide use for this purpose. The scope of boric acid as an antiseptic has been extensive, i.e., in almost every conceivable surgical condition: as a detergent for painful and suppurating **wounds** and **ulcers**; as a basis for injections and ointments of all kinds; in collyria; as an insufflation powder for the ear; to wash out the bladder in **cystitis** and for a similar purpose in **dilated stomach**; as an application to skin maladies. But the toxic effects described under "Poisoning" should always be borne in mind.

Boric acid has been very extensively employed in the treatment of diseases of the eye. Bourgeois, of Rheims, recommends it for **phlyctenular** and **granular conjunctivitis**; Smith, as a wash for **ophthalmia neonatorum**. It has also been used as an ointment between the eyelids after operating for **cataract**; but the drug should be used with caution, and of a strength of not more than 1 per cent., since Noyes has seen a diffuse keratitis develop from a 4 per cent. solution.

In **measles**, too, frequent bathing of the eyes, nose, and ears with a warm, but weak, boric acid solution is to be recommended as beneficial and comforting to the patient.

This drug has, also, been employed in the treatment of **chancroid** as a dusting powder; in **nasopharyngeal catarrh**, especially the troublesome form seldom seen except in children and in **otorrhea**; in chronic **constipation**, by applying the dry powder direct to the rectal mucosa. In a watery 5 per cent. solution boric acid has been extensively employed in

pharyngitis and in mild laryngitis; in aphthæ and other forms of stomatitis, and in ointment form to the urethra for gonorrhea, and also to the pustules of variola to prevent pitting.

Rapid recovery is said to have been obtained in eczema, and also in contagious impetigo, by employing it in glycerole of starch, 1 to 30. In the erysipelas of the newborn, boric acid has been lauded above many other agents.

Saturated solution of boric acid as a wet dressing is almost specific in streptococcus and staphylococcus albus or citreus infection of the skin and cellular tissue, as well as in pemphigus. It is less effective in staphylococcus aureus and entirely without value in gonorrhea, specific inguinal adenitis, chancre, chancroid, pyocyaneus and saprophytic infections, and even harmful in malignant edema, tuberculosis, and impetigo contagiosa. Rest, elevation, and elimination by the bowels, lungs, skin, and kidneys should be carried out conjointly. Ninety-five per cent. alcohol added to the boric solution to make it 15 to 30 per cent. alcohol is of great value. An area should not be incised unless there is a collection of pus and then the incision should be kept inside the limits of nature's walled off zone or distal to it. E. H. Ochsner (Ills. Med. Jour., xxxi, 139, 1917).

SODIUM BORATE; SODIUM BIBORATE; BORAX.—This, the best known, and most generally employed internally, of all the borate salts, has long been alternately lauded and condemned by the medical profession, though it has always retained a *status* in domestic pharmacy and therapeutics. It is soluble, we have seen, in 16 parts of cold water and insoluble in alcohol, though very soluble in glycerin and fats. It has

been found that the addition of a small amount of sugar greatly increases the solubility of borax, and that it will also rapidly liquefy a solution of gum arabic which has become gelatinous from the presence of borax.

According to Dujardin, sodium borate, which as a general rule behaves like the alkalies, should not be associated with the salts of the alkaloids. In mixtures of this kind the patient is likely to take most of the alkaloid in the last dose, with harmful effect.

SODIUM BORATE POISONING.—The phenomena are the same as those caused by boric acid, the latter in fact being the toxic constituent of the salt.

Case of an infant 2 months old born strong and healthy which developed thrush a fortnight after birth. A mixture of borax and honey was applied, which relieved the thrush, but the child developed a liking for it, so that from two to three 4-dram (16 Gm.) boxes were used every week. The author describing the effects says that a progressive wasting had set in, and when he saw the infant there was a marked erythematous eruption on the palmar aspect of the hands and on the plantar aspect of the feet, with distinct desquamation between the toes and the fingers; well-marked urticarial eruption was present on the arms and forearms, but the region between the legs was notably free from eruption. There were tumefaction and tenderness of the abdomen and a raw, pinky redness of the lips, tongue, palate, and throat, with vomiting and looseness of the bowels. The face had a wizened look, the skin was soft and brownish, the eyes were bright, and the joints, especially the knees, tender, swollen, and somewhat stiff. There was no evidence of syphilis or other cause for the wasting and rash except the borax, of which the child had about 10 grains (0.65 Gm.) every day for six weeks. On stopping

the borax and confining the infant to breast milk, together with a little raw-beef juice, it appears to be recovering rapidly. McWalter (*Lancet*, Aug. 10, 1907).

TOXIC EFFECTS OF SODIUM BORATE (BORAX) AS FOOD PRESERVATIVE.—The study of the toxic effects of boric acid submitted on page 591 applies also to borax. An experimental study of the influence of the latter, under the direction of H. W. Wiley, led him to the following conclusion:—

"The most interesting of the observations which were made during the progress of the experiments was in the study of the direct effect of boric acid and borax, when administered in food, upon the health and digestion. When boric acid, or its equivalent in borax, is taken into the food in small quantities, not exceeding $\frac{1}{2}$ gram ($7\frac{1}{2}$ grains) a day, no notable effects are immediately produced. The medical symptoms of the case in long-continued exhibitions of small doses or in large doses, extending over a shorter period, show in many instances a manifest tendency to diminish the appetite and to produce a feeling of fullness and uneasiness in the stomach, which in some cases results in nausea, with a very general tendency to produce a sense of fullness in the head, which is often manifested as a dull and persistent headache. In addition to the uneasiness produced in the region of the stomach, there appear in some instances sharp and well-located pains, which, however, are not persistent. Although the depression in the weight of the body and some of the other symptoms produced persist in the after-periods, there is a uniform

tendency, manifested after the withdrawal of the preservative, toward the removal of the unpleasant sensations in the stomach and head above mentioned.

"The administration of boric acid to the amount of 4 grams per day, or borax equivalent thereto, continued for some time, results in most cases in loss of appetite and inability to perform work of any kind. In many cases the person becomes ill and unfit for duty. Four grams per day may be regarded, then, as the limit of exhibition beyond which the normal man may not go. The administration of 3 grams per day produced the same symptoms in many cases, although it appeared that a majority of the men under observation were able to take 3 grams a day for a somewhat protracted period and still perform their duties. They commonly felt injurious effects from the dose, however, and it is certain that the normal man could not long continue to receive 3 grams per day.

"In many cases the same results, though less marked, follow the administration of borax to the extent of 2 grams and even of 1 gram per day, although the illness following the administration of borax and boric acid in those proportions may be explained in some cases by other causes, chiefly grippe.

"The administration of borax and boric acid to the extent of $\frac{1}{2}$ gram per day yielded results markedly different from those obtained with larger quantities of the preservatives. This experiment, Series V, conducted as it was for a period of fifty days, was a rather severe test, and it appeared that in some instances a somewhat unfavorable result attended its

use. On the whole the results show that $\frac{1}{2}$ gram per day is too much for the normal man to receive regularly. On the other hand, it is evident that the normal man can receive $\frac{1}{2}$ gram per day of boric acid, or of borax expressed in terms of boric acid, for a limited period of time without much danger of impairment of health.

"It is, of course, not to be denied that both borax and boric acid are recognized as valuable remedies in medicine. There are certain diseases in which these remedies are regularly prescribed, both for internal and external use. The value which they possess in these cases does not seem to have any relation to their use in the healthy organism except when properly prescribed as prophylactics. The fact that any remedy is useful in disease does not appear to logically warrant its use at any other time.

"It appears, therefore, that both boric acid and borax, when continuously administered in small doses for a long period, or when given in large quantities for a short period, create disturbances of appetite, of digestion and of health."

THERAPEUTICS.—As an application to mucous membranes, because of its mildly antiseptic and soothing effects, borax in solution is very useful and often serves a better purpose than more pronounced astringents or local stimulants. Especially is this true of some of the lesser diseases of the eye and nasopharynx, the milder forms of **conjunctivitis**, certain forms of **rhinitis**, **ulcerative stomatitis**, etc. In the various milder forms of stomatitis in infants, borax and honey constitute a valuable household remedy. Sodium borate in camphor water secures a pleasant,

harmless, and grateful collyrium that may advantageously be employed, either alone or in connection with other remedies, in most inflammatory conditions of the eyes.

Sodium borate in solution may be employed topically to dissolve the pellicles of the epidermis joined together by sebaceous matter, thereby acting as a detergent; in **eczema** and other eruptions attended with **pruritus** due to the accumulation of products of the sudoriparous glands the salt is often most effective. Congenital **ichthyosis** is often benefited by washes of sodium borate.

In **erysipelas** Sevestre employs baths at 93.2° F. containing 16 ounces (500 c.c.) of sodium borate, which, he claims, lowers the temperature and tends to heal the eruption.

Both borax and boric acid have been recommended as injections in **dysentery**, but the solution should not be strong lest absorption and intoxication occur.

In **infantile diarrhea** daily irrigations of the larger bowel have been found most beneficial during the height of the disorder, borax, 1 dram (4 Gm.) to a pint (480 c.c.) of warm water, being employed.

That sodium borate has some action upon the central nervous system is apparent, but this is so ill understood that it is impossible to formulate any definite physiological basis for its internal administration. It has been tried in **epilepsy**, but is inferior to the bromides, while the chances of an eruption soon developing are greater. Borax has also been recommended for several nervous disorders, including **locomotor ataxia**, **paralysis agitans**, etc., but it is inferior to other remedies available.

Sodium borate is endowed with a special affinity for the genitourinary organs. In some cases it relieves **uterine hemorrhage** with surprising promptness; it has also proved very useful in **chronic cystitis** in 5-grain (0.3 Gm.) doses three times daily, coupled with washing out of the bladder with small quantities—a couple of ounces of a 2 grain (0.13 Gm.) to the ounce (30 Gm.) solution at 105° F. Stronger solutions, 5 grains (0.33 Gm.) to the ounce (30 Gm.), have also been found advantageous in **leucorrhea** and **gonorrhea**.

L. T. DE M. SAJOUS,
Philadelphia.

BRIGHT'S DISEASE.

ACUTE NEPHRITIS, or **ACUTE PARENCHYMATOUS NEPHRITIS**, also termed sometimes, though infrequently, **Acute Bright's Disease**; **Acute Diffuse Nephritis**; **Exudative, Catarrhal, Tubal Desquamative, and Glomerulonephritis of Acute Course**.

DEFINITION.—An acute inflammation of the kidneys, and either of a mild, severe, or grave character. It may be more or less diffuse in nature. Three varieties of acute renal disease are described by Delafield under the term acute Bright's disease: (1) acute degeneration of the kidneys; (2) acute exudative nephritis, and (3) acute productive nephritis.

SYMPTOMS.—The onset is sudden, as a rule, but varies with the exciting cause of the nephritis. Chilliness, nausea and vomiting, pain in the back, and, within twenty-four hours, dropsy are seen in some cases. Children are subject to convulsions (uremic), and in severe cases adults are no less liable. Fever may be present, but it is neither constant nor high. The early appear-

ance of edematous puffiness of the eyelids and face, and of pallor of the skin, is characteristic. Soon, and sometimes at first, a swelling occurs about the ankles and legs, and in severe cases dropsy involves the whole body. The scrotum, penis, or labia may, in such cases, become enormously distended, the skin presenting an almost translucent appearance. The blood-pressure is apt to be raised, especially in children.

In the acute nephritis of young children the blood-pressure is often raised to a marked degree. This fact has failed to be recognized by pediatricians. The pressure for children at different ages was first obtained by the writer by working out the averages on a series of 170 cases between the ages of a few months and 12 years. Observations were then made on 9 cases, 7 of which were cases of acute nephritis, and 2 were chronic, with acute symptoms superadded. This showed that in children suffering from acute nephritis the blood-pressure is raised, and that this rise may be very great. In 3 out of the 7 acute cases the hypertension was very marked. This fact is of diagnostic value, as in no other disease of childhood is there to be found the same high range of blood-pressure. Those cases having the highest pressure were those in which only a trace of edema was noticeable, and also it was noted that in these same cases the quantity of blood in the urine was very great, the explanation being, probably, that the greatly increased blood-pressure had caused a rupture of the renal capillaries. Lennox Gordon (*Archives of Pediatrics*, vol. xxviii, p. 343, 1911).

There may occur a diffuse nephritis in which the glomeruli are primarily involved due to a general sepsis arising from some focus of infection. If this focus is discovered early and removed the nephritis may be recovered from completely, but in many cases its continued presence makes the nephritis progressive. The con-

dition is a true nephritis, as the lesions are typically inflammatory.

Three forms of the disease can be recognized: Acute, subacute and chronic.

One of the commonest focal infections, especially in the chronic types, is a chronic suppurative tonsillitis without material enlargement of the tonsils and due to a diplostreptococcus. W. Ophüls (Jour. Amer. Med. Assoc., Oct. 13, 1917).

A gallop sound was the first sign to call attention to the acute nephritis in cases observed by the writer. In a girl of 12, there was complete asystole when first seen; she was cyanotic, and almost pulseless. The gallop sound was due to an enormous dilatation of the heart. There was also bronchopneumonia, however, and the child seemed to be convalescing, when purulent pleurisy set in, ending in death. Ponce de Leon and Morquio (Arch. Latino-Amer. de Pediat., May-June, 1920).

Often local symptoms are absent, as pain and tenderness in the lumbar region; they are never marked.

Micturition may be frequent and accompanied by a slight burning and vesical tenesmus, due to the concentrated urine.

In severe dropsy the tense, dry skin may become sensitive or even painful on pressure. Bodily movements are often painful and difficult in cases of marked anasarca. Uremia may be heralded by intense headache and backache.

In a report drawn up by the Medical Research Committee on War Nephritis working in France the writers describe the onset of the disease as usually insidious. The first indication in those doing heavy manual work was increasing shortness of breath; in sedentary workers headache.

The edema present tended to clear up rapidly usually, with well marked diuresis and often heavy sweats. The

albuminuria then usually improved considerably. Hyaline casts were the most abundant, granular next and epithelial last. A moderate rise of systolic blood-pressure was almost invariably present during the period of edema, falling to normal or below as the edema subsided. There was frequently a marked difference in the height of the morning and evening pressures, the latter being the higher. In most cases a definite hydremia could be demonstrated. Although cardiac symptoms were frequent, the only physical sign was a temporary enlargement of the heart to the left in 23 per cent. On discharge from hospital, however, the heart appeared normal. Chemical investigations showed no differences in kind between this and ordinary nephritis. The urea in the blood was usually increased, the chlorides variable. In convulsive cases which recovered, the blood urea was not appreciably raised, whereas in a fatal case of uremia it was exceedingly high. De Wesselow and MacLean (Lancet, Sept. 14, 1918).

Among 50,000 men whose urine was examined during the war, the total percentage of albuminuria (unaccounted for by pus, spermatozoa, blood etc.) was found to be about 5 per cent. The average percentage of urines found to contain casts was 1.87; of this number 0.84 per cent. had definite epithelial casts, while in 1.03 per cent. hyaline casts only were found. The writer is fairly certain that at least 132 cases of definite nephritis were returned from among the group of 50,000 men previously examined for albumin. As certain of the other 29 cases were also, probably, suffering from nephritis, the total 161 cases may be taken as the maximum number of individuals who developed nephritis within 9 months after being examined at the base. Out of the 161 patients returned as nephritis or albuminuria, only 28 suffered from albuminuria just before going to the front. MacLean (Brit. Med. Jour., Jan. 25, 1919).

A urinary examination is always necessary, as in mild cases the renal condition may be overlooked. There may be no further symptoms than a general malaise.

Acute nephritis is frequently accompanied by a marked psychic depression which is important for differentiation. The writer noted this symptom in many cases and also in himself. Although comprehending and feeling as usual, free from headache, dizziness, and tinnitus, complete apathy and indifference to the environment became noticeable. There are no special symptoms and yet one does not feel well. This condition is explained by the albuminuria, oliguria, and edema which develop in the course of a day or so, with the other symptoms of acute nephritis. Janovsky (*Revue de méd.*, Aug., 1908).

In a recent case of mercuric chloride poisoning, the anuria was accompanied by coma alternating with delirium, and there was 0.3 Gm. of urea per thousand in the blood. Death occurred the fifth day without edema or uremic symptoms. S. Pascual (*Medicina Ibica*, Jan. 18, 1919).

The urine in acute nephritis furnishes distinctive characteristics. The total quantity passed in twenty-four hours is diminished, and may even be very scanty, varying from 5 to 25 ounces (150 to 740 c.c.). There may be suppression in cases of toxic origin, when an acute degeneration or necrosis of the renal epithelium occurs, and in the very severe exudative inflammations.

The specific gravity is early increased to 1025 or more, though later it may fall to 1015 or 1010. The color is darker than normally and is usually smoky red, or reddish brown, according to the amount of blood contained. A more or less abundant flocculent sediment appears on standing, if the normal morphological constituents are present in great quantity.

Some red blood-corpuscles and renal epithelium are found microscopically, together with the characteristic hyaline, blood, and epithelial tube-casts. The urine is acid in reaction, and on boiling throws down a thick, curdy precipitate of albumin, which varies in weight from $\frac{1}{4}$ to 1 per cent. The urea is diminished.

The molecular concentration or osmotic pressure of the urine is usually reduced, so that the freezing point (cryoscopy) is 1° or less than 1° C. (instead of the normal 1.3° to 2.3° C.) below that of distilled water (0° C.).

As an aid in diagnosis, cryoscopy may foretell the onset of an attack of uremia in a nephritic before any of the usual clinical manifestations are present. For this purpose it must be systematically employed, daily observations made of the freezing point of both blood and urine. One can thus differentiate, with some degree of certainty, between uremic coma and that due to cerebral hemorrhage, tumor, alcoholism, epilepsy, opium poisoning, hysteria, and malingering. (Tieken.) The procedure may enable one to employ more energetic prophylactic measures before the uremic attack, as well as to determine the efficiency of the treatment of nephritis. It may help to determine the advisability of venesection and subsequent transfusion. If the freezing point of the blood falls and that of the urine rises in spite of treatment, the prognosis is grave. If the blood shows an elevation and the urine a depression, the prognosis is correspondingly more favorable.

There may also be other symptoms during the course of acute Bright's disease, as those of hydrothorax, ascites, and hydropericardium, in cases in which great general edema is present. The first-named condition is bilateral and gives rise to dyspnea; the second increases the dyspnea by pressing the diaphragm upward, and the last impedes the heart's action. Strümpell

describes a form of pneumonia that sometimes develops in severe cases of acute nephritis,—a “stiff inflammatory edema,”—midway between lobar and broncho-pneumonia. There may also be edema of the conjunctivæ, soft palate, and larynx.

The pulse is often hard and tense, and, though slow at first, it may become accelerated later. Cardiac hypertrophy may be present in a slight degree. The aortic second sound is accentuated.

Two instances of bradycardia in nephritis. The first case was in a woman of 28 with acute nephritis which had come on in the midst of good health; the pulse grew progressively slower, from 72 to 44, evidently the result of irritation of the regulating system of the heart, there being no auriculoventricular dissociation. The second patient had chronic nephritis, and the bradycardia was likewise apparently of nervous origin in this case. Danielopolu (*Arch. des mal. du cœur*, etc., July, 1911).

In a large number of cases with symptoms of severe acute gastroenteritis due in particular to renal insufficiency, encountered in a French military hospital, the illness came on suddenly or gradually, the initial symptoms being mild diarrhea, nausea, headache, and backache, without fever. In the more rapid cases copious vomiting appeared, with grayish or yellowish serous stools, severe cramps, violent headache, oliguria, and marked prostration. Slight cyanosis was noted on admission, the extremities were cold, the pulse could not be counted, and the patient hardly answered when spoken to. A few of these patients died within 1 or 2 days. In the majority, the earlier violent symptoms subsided under rest, restriction to water, isotonic lactose solution, and heart tonics, but the patient's fate depended on whether the kidneys could recuperate and regain a salutary diuresis, or were unable to do so. In a slower form of the affection, the initial mani-

festations were followed by short paroxysms of diuresis alternating with diarrhea. Blood, stool, and bile cultures were always negative. In the etiology, most stress is laid on severe infections earlier in life causing a latent renal insufficiency, with physical overwork as the immediate exciting factor. C. Mattei (*Paris méd.*, Mar. 17, 1917).

Epistaxis appears occasionally, and subconjunctival hemorrhages sometimes follow unwitnessed uremic convulsions. Dryness and uremia of the skin form a constant condition. Uremic manifestations may supervene at any period in the disease, appearing early in the most severe cases, with intense headache and backache, vomiting, and convulsions.

The above may be considered a description of the common form of acute nephritis resulting from exposure; the clinical course differs somewhat in other cases. Occurring as a complication of the infectious fevers, except scarlatina, acute nephritis may be characterized by the very slight degree, or even by the absence, of dropsy. Albuminuria, hematuria, anemia, and uremia mark the graver affections. In scarlatinal nephritis, however, anasarca is common, and a slight edema, at least, is quite constant. Mild affections show simply a slight quantity of albumin and a few hyaline casts, indicative of the parenchymatous degeneration. The typhoid state may follow the subsidence of the acute toxic symptoms in cases of degenerative nephritis due to mineral poisoning; this is marked by prostration, muscular twitchings, stupor, coma, and death. Hematuria may be pronounced in the so-called nephrotyphoid condition, in which typhoid fever begins with marked symptoms of acute nephritis.

Report of 15 cases, 9 fatal, of an association of severe icterus with

nephritis. Characteristic was the initial severity and rapid course. There appeared to be no element of contagion nor epidemicity. The symptomatology is strikingly uniform. The patients are stricken suddenly with fever, chills, headache, vomiting, diarrhea, and oliguria (fever may be absent). There was nervous adynamia and a stuporous state suggesting typhoid. There may be neuritic pain in the lower extremities, precordial or epigastric anxiety, and an anxious facies. Icterus may appear in a few hours or a few days, and is of the classic choluric type: the stools are, as a rule, not decolorized. The participation of the liver is shown by hemorrhages, which in some cases appear in crops. There is cessation of fever after several days. Albuminuria shows no typical behavior. The outcome depends, however, on the activity of the kidneys; if diuresis can be established the patient has a better chance of survival. Acute cachexia may end in death from coma. Merklen (*Revue de Méd.*, Mar., 1916).

The nephritis of pregnancy, as a rule, is gradual in its onset. The albumin increases in quantity from month to month, reaching a high percentage during the eighth and ninth. Some hyaline casts are found, but otherwise there are few morphological elements. Red blood-corpuscles rarely may be seen in the urine. Up to the time of delivery the danger of eclampsia is constant, but recovery is rapid in uncomplicated cases after the birth of the child.

In acute (productive) nephritis, where there is a tendency to the formation of patches or wedges of fibrous tissue, there is a higher fever, there are cerebral and circulatory disturbances of a typhoid nature, as well as anemia, dropsy, and a highly albuminous urine, even though there be no blood-corpuscles and few casts. Dropsy is most

marked in the legs. There are a progressive and rapid loss of flesh and strength, dyspnea, vomiting, diarrhea, and convulsions or coma and end in death. Milder cases last from two to four weeks, and apparently recover; albumin and casts persist, however, until another and a similar attack occurs after an interval of weeks or months. Thus, the first acute attack is subject to chronic recurrence, until a fatal seizure takes place.

In children ocular complications are uncommon in cases of acute nephritis, and when they occur they usually assume the form of an inflammation of the optic papilla. Retinal complications are apparently much less frequent in parenchymatous than in interstitial nephritis. The ophthalmoscopic signs do not appear to differ either quantitatively or qualitatively in the two forms of chronic nephritis. Detachment of the retina may occur as a complication of retinitis in childhood. The significance as regards duration of life is as unfavorable in the renal retinitis of children as in that of grown-up persons. Stevenson (*Brit. Med. Jour.*, Sept. 21, 1907).

In 26 recent cases of a so-called rheumatic inflammation of the eyes the writer found 1 instance of arthritis deformans, 1 of acute muscular pain that yielded quickly to salicylates, 3 other cases (one 24, one 60, one 65 years of age) that reported some recurrence of muscular pain. The other 21 patients gave no history of symptoms that could be called rheumatic. All required distance glasses; 16 had no glasses; 10 were wearing incorrect distance glasses. There was marked eye-strain in all.

The most notable feature, however, was that more or less nephritis was found in all except 1, and in that case only one examination of the urine could be made. In 7 of these cases the renal inflammation was apparently only parenchymatous. Austin O'Malley (*Amer. Med.*, Nov., 1911).

The eye changes in trench nephritis were studied by the author. Almost invariably marked retinal congestion, with large pulsating veins, were present. Some weeks later, definite nerve swelling, accompanied by patches of retinal exudation, were seen. The spots of exudation were generally near the disk and in the macular area. Hemorrhage was not common. Small areas of edema were noticed, especially along the veins. The condition is probably an acute congestion resulting from some specific toxin. The exudation probably clears up in most cases. The condition is probably allied to the acute retinitis of pregnancy, scarlatina, and acute uremia, and should not be confounded with the retinitis of chronic kidney inflammation. Kirk (Brit. Med. Jour., Jan. 5, 1918).

DIAGNOSIS.—Acute Bright's disease can hardly be overlooked when the urine is carefully examined chemically and microscopically. The eclampsia of pregnancy can, however, be recognized only by repeated examination of the urine, especially during the last months of pregnancy. Acute nephritis should be suspected, and the urine examined, in every case showing pallor of the skin and puffy eyelids, whether general prostration of the health is apparent or not.

Among 50,000 soldiers, the total percentage of albuminuria (unaccounted for by pus, spermatozoa, blood, etc.), was about 5 per cent. The average of urines found to contain casts was 1.87; of this number 0.84 per cent. had definite epithelial casts, while in 1.03 per cent. hyaline casts only were found. Out of 161 patients returned as nephritis or albuminuria, only 28 had albuminuria before going to the front. MacLean (Brit. Med. Jour., Jan. 25, 1919).

The typical symptoms of acute exudative nephritis, as commonly seen when the condition is due to cold or

occurs in scarlet fever, are the following: Headache, restlessness, muscular twitching, nausea and vomiting, a tense pulse, moderate fever, dropsy, and anemia. Tube-casts and albuminuria are constant. It should be borne in mind that slight albuminuria occurring in the course of pregnancy or during any of the fevers, without casts, is not a true nephritis, although the latter may be a more or less remote consequence of the glandular degeneration of the renal epithelium associated with the febrile albuminuria. In addition to the presence of albumin and hyaline and cell-casts, however, a diminished quantity of sooty-looking urine and the discovery of red and white blood-corpuscles will render the diagnosis positive. The history of the case and the causal factors are also to be considered.

ETIOLOGY.—Acute nephritis more often appears before than after the middle time of life, though it may occur at any time. Males are more often attacked than females.

Occupations necessitating exposure to cold and wet offer special predisposing conditions. The long-continued use of alcohol will also, as a rule, prove a predisposing cause of acute Bright's disease.

From a clinical study of 460 cases of chronic alcoholism the writer concludes that alcohol when taken daily, as it is by chronic inebriates, dipsomaniacs, or drinkers, is not an irritant to the kidneys. When nephritis occurs in a chronic alcoholic, it is probably due to some other concomitant toxic agent, and not to alcohol. Overeating, acute intoxicants, exposure to colds, autointoxications, infections either manifest or latent, and some metabolic disorders as yet unknown are the real causative factors of nephritis.

Alcohol when taken by drinkers as food or stimulant, such as seen in

chronic alcoholism, is a diuretic. Those tissues which eliminate alcohol are least affected by it. This applies to the lungs and especially to the kidneys. While an intoxicant, alcohol is also a detoxicant, ridding the body of various deleterious catabolic products.

The comparative integrity of the kidneys in alcoholics may be due to the fact that the renal cells contain very few lipoids and lecithins, and that, therefore, they are not at all acted on by the narcotic molecule. J. F. Hultgen (*Jour. Amer. Med. Assoc.*, July 23, 1910).

Among the exciting causes of acute diffuse nephritis are:—

1. Those acting on the skin, as cold, dampness, extensive burns, and chronic skin diseases. It is often difficult to determine the relative influence of alcoholic excesses and the exposure incident thereto. Acute intoxication from beer-drinking may result in an acute nephritis, but it is yet likely that in most cases the exciting cause is the cold acting upon the individual in his exposed and maudlin condition. Acute nephritis may also be caused, at times, by exposure to cold and wet apart from and in the absence of alcoholic indulgence; in such cases it is to be presumed that there is an inherent weakness of the kidneys, or a susceptibility rendering these organs the vulnerable point in the system.

The physiological toxic agents embrace the poisons of the acute infections; in a majority of cases, however, scarlet fever is the primary affection. Usually the nephritis appears during the second or third week of convalescence, though it may supervene at the height of the disease.

The most common cause of nephritis of childhood is that which follows scarlatina; but it may be caused by any of the infectious diseases of

childhood. Among these are measles, diphtheria complicated with a mixed infection, severe infections of the tonsils and pharynx that are not caused by the Klebs-Löffler bacillus, intestinal intoxications, appendicitis, etc. In some cases the child has had scarlatina some years before, and the kidneys have been impaired, and thus form a place of least resistance for new infection. Under such circumstances exposure to cold has an important etiological bearing. In adults the causes of nephritis are often poisons formed within the body, as in arteriosclerosis and gout. These are comparatively rare in children, in whom the causes come from without. Gastrointestinal and cutaneous troubles are the chief causes from within. These infections occur in children who are congenitally delicate, or are weakened by some previous disease. Mumps, erysipelas, and rheumatism may cause nephritis. The symptoms are malaise, fatigue, and headache, coming on suddenly or slowly, sometimes accompanied by convulsions or coma. The amount of urine is small; it is high-colored, and thick with sediment. Edema is marked, and lumbar pain severe. The pleural cavities should be carefully examined for fluid. The edema depends not on the retention of water, but of chlorides and urea. The heart is quickly affected, with increased arterial tension, dilatation, and disturbed rhythm. Hutinel (*Bull. méd.*, Jan. 29, 1910).

Report of 2 cases of traumatic nephritis in young women who had been kicked in the abdomen and trampled upon. In the first, the acute nephritis soon subsided. In the second case the urine contained much blood from the first, and urination was not painful as in the first case. By the end of a month there was no blood but many casts and much albumin, and on re-examination 10 months later, the urine showed unmistakable evidence of chronic nephritis. M. Castañeda (*Cronica Med.*, May, 1917).

Stress laid on gastrointestinal toxemia as a cause of nephritis. The author refers to 3 cases in which the arresting feature was an abnormality in the gastrointestinal canal. The first had pyorrhea, dilatation of the stomach, with a history of gastric inflammation, and the tongue bore evidence, from the enlargement of the papillæ, that there was an abnormal condition of the ileum. The second had septic ulcers in the mouth and on the tongue, and a constant discharge of purulent material from the nose, which in all probability was the cause of the septic condition in the upper part of the alimentary canal. The third case had equally striking gastro-intestinal symptoms, with definite physical signs pointing to a gastro-intestinal cause. In a fourth case of nephritis there was enormous distention of the colon and a large amount of ascitic fluid. The patient had suffered for 2 years from severe and continuous diarrhea, with foul-smelling motions. A posterior colostomy was done and the symptoms were greatly relieved, but the patient later died from sudden heart failure. In each of these cases the presence of toxemia was demonstrated by a pronounced *tache cérébrale*. William Watson (Glasgow Med. Jour., July, 1918).

2. Acute nephritis may also be the result of other of the infectious fevers (small-pox, typhus, typhoid, relapsing fever, cholera, diphtheria, yellow fever, measles, chicken-pox, erysipelas, septicopyemia, acute lobar pneumonia, cerebrospinal meningitis, dysentery, acute articular rheumatism, and tuberculosis; syphilis is rarely a cause).

Study of 28 cases of pneumococcal nephritis in children, 1 of which is original. The writer distinguishes 3 varieties of pneumococcal nephritis:

1. Albuminuria in the course of pneumonia, which is a mere episode in an infectious disease without any special gravity. 2. A severe form characterized by the usual symptoms of acute

nephritis. In the great majority of cases the pulmonary lesion is a bronchopneumonia. This is the most frequent variety, since 22 of the 28 cases were fatal. 3. A mild form affecting older children and associated with lobar pneumonia. Anatomically pneumococcal nephritis is characterized by lesions of the renal parenchyma, the convoluted tubules being principally affected. V. Schmarine (Brit. Jour. of Dis. of Children, Sept., 1911).

Nephritis occurs often enough in recently acquired syphilis to justify reduction of salt and a milk-vegetable diet during the first stage. In a case of nephritis in tertiary syphilis, no benefit followed 3 weeks of dieting, and when mercurial and iodide treatment was pushed, in 2 weeks there were no further signs of dropsy or headache. In a case of hypertension complicating the nephritis, specific medication increased dyspnea and caused symptoms of lung congestion. After repose, restriction to milk, wet cupping and small venesection, the man was enabled later to stand cautious resumption of specific treatment. M. del Sel (Prensa Med. Argentina, Oct. 30, 1917).

The term trench nephritis is a misnomer, for it is unnecessary to have lived in the trenches to suffer the affection. In most instances the individuals had previously been robust and without ailment. A few had had an antecedent sore throat or bronchitis. Edema was commonly the earliest manifestation. Headache was not uncommon and nocturnal dyspnea occurred in 78 per cent of cases. A rise in blood-pressure was noted in about one-half the cases. In a number of instances the nephritis was recurrent, the individual giving a history of previous illness having no relation to the military conditions. In the series reported 6 per cent. had convulsions. Only 1 case died, a recurrent one with small granular kidneys. The condition probably has its basis in infection and is of the nature of a glomerulonephritis. Ru-

dolph (Can. Med. Assoc. Jour. vii, 289, 1917).

History of recent tonsillitis, acute rheumatism, or severe chilling noted in a large proportion of cases of acute nephritis in soldiers in active service; in others there was pyorrhea, otitis or furuncles, but in fully 50 per cent. of the cases its origin was obscure, notwithstanding the more or less epidemic character. There is much to sustain the assumption that war nephritis is a hitherto undescribed infectious disease. It seems to have been known in Russia in times of peace, and also during preceding wars. The blood-vessels bear the brunt of the attack, and the vascular lesions are apt to retrogress completely with early and complete recovery. Privations and vermin probably are etiological factors. Ceconi (Riforma Medica, Jan. 26, 1918).

Report of 160 cases of war nephritis. The chief predisposing factor was age, five-eighths of the patients being over 30. The season appeared to make little difference. In 16 cases there was a history of previous renal disease; in 12 of scarlet fever, and in 5 of diphtheria. The disease is probably of infective origin, since the first stages are often marked by fever and frequently associated with influenza, bronchitis, trench fever, gastroenteritis, boils, tonsillitis, or other infective condition. In addition, there are symptoms of irritation of the urinary tract similar to those caused by the *B. coli communis*, and the condition is very similar to scarlatinal nephritis. The disease cannot be ascribed to any small agent, and the absence of epidemiology would seem to negative the assumption that it may be due to an infective agent as yet undiscovered. The greater incidence in the army as compared with civil life is explained by (a) sensitiveness of the renal tissues, due to fatigue and exposure, (b) greater liability to the entrance of infective agents into the blood-stream and thence into the kidneys.

The diastolic interval was shortened in about 50 per cent. of cases. More frequent still was a ringing accentuated second sound at or near the apex. Pulmonary physical signs may be bronchial or basal. Twelve cases manifested uremic symptoms; 4 of these died; 2 of the deaths were due, however, to concurrent bronchitis. As a means of diagnosis, the author recommends the salicyl-sulphonic acid test. The mortality in the series was 3.75 per cent. The most dangerous type is that in which intense nephritis occurs with severe bronchitis. C. F. Coombs (Lancet, Apr. 6, 1918).

Five cases of acute nephritis due to typical impetigo contagiosa. The condition may be just as severe as that following scarlatina. The risk of nephritis, even in efficiently treated cases, is quite as great as in scarlatina, and impetigo explains many obscure, sudden and acute cases of nephritis in children. Possibly many cases of so-called "trench nephritis" in soldiers are the result of an impetiginous pediculosis or scabies. Stiell (Pract., Apr., 1918).

There is a type of acute infective nephritis involving multiple, small or large areas, which, as a rule, proceed to abscess formation. These areas are for the most part situated in the cortex. The infection is usually unilateral. The lesions may resolve or leave the kidney so damaged that complete recovery is impossible and may serve as a foci for further infection. The commonest infecting organism is a member of the *Bacillus coli* group, but other organisms, as the staphylococcus and *B. typhosus*, may produce similar lesions. The infection is in most cases probably lymphatogenous or hematogenous, and in some cases of *Bacillus coli* infection some abnormal condition of the gastro-intestinal tract, seems to play a distinct part. There are frequently no demonstrable lesions of the genitourinary tract. Treatment may be palliative, but operation may be necessary. If nephrec-

tomy is performed early the prognosis is good. Campbell and Rhea (Surg., Gynec. and Obstet., Dec., 1918).

It may also supervene as a primary condition, and the brunt of the attack may be sustained either by the kidney, rather than by any other part, or by the organism as a whole, as in the fevers. Mannaberg has described such cases, and has demonstrated the presence of streptococci in the urine.

3. Chemical toxic agents include turpentine, cantharides, carbolic and salicylic acids, potassium chlorate, iodoform, the mineral acids, and inorganic poisons, such as phosphorus, arsenic, mercury, and lead. Acute renal inflammation may be caused by the excessive ingestion of highly acid, spiced, or adulterated foods (as from salicylic acid and lead chromate). Balsam of Peru, used too freely in the external treatment of scabies, has caused a number of cases.

The kidney reacts differently toward certain diuretics, according to the toxic agent which is used to induce the nephritis. Chrome salts, sublimate, and uranium nitrate are toxic agents which attack first the tubular epithelium and leave at first the vessels undamaged. In the early stages of this tubular form of nephritis salt solution and caffeine, when ingested, cause an increase in the volume of the kidney with diuresis. Cantharidin and arsenic, on the other hand, attack primarily the blood-vessels of the kidney and set up a vascular form of nephritis. In the early stage of this vascular nephritis, neither salt solution nor caffeine produces any increase in the volume of the kidney or diuresis. The ability of a substance to produce diuresis seems, therefore, dependent upon the ability of the blood-vessels of the kidney to react to stimuli. Hedinger and Takayasu (Deut. Arch. f. klin. Med., Bd. xcvi, 1909).

Experimental nephritis produced in dogs with cantharidin, arsenic, diphtheria toxin, and potassium chromate. There was retention of the non-protein nitrogen, urea nitrogen, and chlorides in the blood, and in addition, acidosis. Some dogs showed symptoms resembling uremic coma. Sodium bicarbonate, given by stomach tube, diminished the acidosis. In the milder grades of the disease, the action of the same amounts of poison was variable in different animals. Kingo Goto (Jour. Exper. Med., Mar., 1918).

4. Pregnancy may act as a cause of acute nephritis (gravidarum). In such cases it usually appears in primiparae, in the last months of gestation, and is probably the result of renal engorgement due both to mechanical pressure and to nutritive disturbances in the kidney, owing to the altered blood-condition.

5. Latent chronic nephritis may form the cause of a manifest acute nephritis.

Details respecting the urine findings in 10 football players, 12 wrestlers, 27 athletes after their exercises, and a number of others, all showing that the urine sediment after these exertions resembles the sediment in severe nephritis. Half an hour's wrestling by a robust and healthy individual will bring fat into the sediment of the urine just as is observed in chronic nephritis, but evidently it is merely the result of the changes induced in the circulation. Christensen (Hospitalstidende, Aug. 11, 1909).

Acute nephritis results from acute tonsillitis far more often than is generally believed. The symptoms ordinarily are not manifested until some time after the inception of the disease. The nephritis is of the hemorrhagic type and differs from that of scarlet fever in that pyrexia, edema, and oliguria are not marked symptoms of the disease. In addition, it follows the angina and is not concomitant as in scarlatina and

diphtheria. Judging from the course of the case reported, there may be many in which a mild nephritis occurs incident to an amygdalitis, which goes on to resolution without patient or physician being conscious of its presence. Loeb (*Jour. Amer. Med. Assoc.*, Nov. 12, 1910).

PATHOLOGY.—There is a considerable variation in the anatomical changes in and the appearance of the kidneys, according to the degree of involvement. Between the very mild and grave cases there is an intermediate series of continuously more marked pathological changes dependent upon the amount of poisonous material circulating in and eliminated by the kidneys, as well as upon the intensity and duration of its toxic action.

There may be no microscopical change in the mildest cases. As a rule, however, the kidneys are slightly enlarged, swollen, and somewhat softened, though these conditions are more evident when the interstitial exudation is abundant and inflammatory edema is evident. On section the organs may appear red and congested or they may be pale and mottled. In the former case hemorrhages may appear beneath the capsule (acute hemorrhagic nephritis); it is more usual, however, to see red, hyperemic patches alternating with opaque and whitish portions, both on the outer and the cut surfaces. Especially is the cortex swollen, turbid, and pale or slightly congested in the mildest cases; in severe attacks it is deeply mottled (red and pale glomeruli) or hyperemic. The surfaces are smooth and the capsule non-adherent. The pyramids usually show an intense-red color.

Acute nephritis in children is found following three sets of conditions: 1, alterations, temporary or permanent, in the skin, interfering with its

excreting functions; 2, the ingestion of certain irritants; 3, in the course of certain acute infections. There are also cases of unknown origin. The writer analyzed 107 cases of acute nephritis from ten years' records of the Middlesex Hospital, and found the frequency to be much greater than is generally acknowledged in textbooks. While scarlet fever was more common in the first ten years of life, he did not find it very fatal in children. Voelcker (*Brit. Med. Jour.*, Sept. 21, 1907).

In the very mild cases, already referred to, changes may be noted microscopically that are not visible to the naked eye, there being simply a cloudy swelling or a granular (parenchymatous) degeneration of the epithelium of the Malpighian tufts, Bowman's capsule, and of the uriniferous tubules of the cortex. In the absence of exudative changes in the interstitial tissue, however, this cannot be called true acute nephritis. The acute parenchymatous degeneration may be limited almost exclusively to the glomeruli, as in some cases of scarlatina, and from this fact has arisen the term "glomerulonephritis." The nuclei are either swollen or absent; the cells are swollen, opaque, and irregular in shape, and the cell-contents are granular (albuminoid or fatty). The death of the cells—owing to coagulation necrosis or disintegration, desquamation, and hyaline degeneration of masses of the cells in the tubules—marks a further stage in the process. Acute degenerative changes are frequently found in the acute infectious diseases, or when inorganic poisons have been introduced into the body. In phosphoric poisoning there may be an actual fatty degeneration of the epithelium, either proceeding from the cloudy swelling or occurring as an independent development. In severe

cases a rapid necrosis of the cells is also met with.

An experimental study of acute nephritis showed that potassium chromate, uranium nitrate, and corrosive sublimate cause extensive tubular injury without evidence of vascular injury, while arsenic and cantharidin produce but little injury to the tubules, but cause anuria. Physiologically, these two types represent tubular and vascular nephritis. In the tubular form the output of nitrogen is considerably diminished. In the vascular nephritis the nitrogen elimination is greatly increased. Pearce, Hill, and Eisenberg (*Jour. Exper. Med.*, March, 1910).

True acute nephritis exhibits not only changes in the parenchyma (epithelium), but also an inflammatory exudate between the tubules, consisting of serum, leucocytes, and red blood-corpuscles. In some places the kidneys show only a slight cellular infiltration of the intertubular tissues. In others the interstitial tissue is swelled by the coagulated serofibrinous exudate, many leucocytes, and some erythrocytes, besides the desquamation of necrotic epithelial cells and the presence of hyaline casts in the tubules. The inflammatory exudate collects, also, in the Malpighian bodies and tubules. The tubules may be dilated and choked with degenerated cells, or more frequently the straight tubules are clogged with hyaline casts. The lining epithelium, especially in the convoluted portion of the tubules, is often flattened. The white blood-corpuscles infiltrating the stroma of the kidneys are collected in foci in the cortex, and not, as a rule, equally diffused.

The writer urges that the high arterial pressure is primary and the hypertrophy of the heart a secondary phenomenon in acute and chronic nephritis, the elevation of the blood-pressure being a regulating phenom-

enon—the work of the glomeruli. Whether this occurs by chemical or reflex means is still a question. The arterial pressure in his experience always rose when uremia was impending or established. Patients leading tranquil lives, on a light diet, kept the blood-pressure at a moderate height. Change to a mixed diet, especially when meat and salt were taken, always increased the pressure. Loeb (*Deut. Archiv f. klin. Med.*, Bd. lxxxv, Nu. 3 and 4, 1906).

There is in the blood and in the urine of persons suffering from nephritis a substance analogous to adrenalin which produces a dilatation of the pupils of frogs, is more or less constant, and is found in relation with a rise of the blood-pressure. In other diseases its presence is exceptional, save in arteriosclerosis, in which it is almost constant. Macaroff (*Presse médicale*, Jan. 13, 1909).

The writer explains the rise of blood-pressure in nephritis to the presence of adrenalin in the blood of patients suffering from nephritis noted by Wiesel and Schur. He suggests that the renal inflammation causes an obstruction to the flow of blood in both kidneys, and that as a result of this there is an increased flow of blood in the inferior suprarenal artery, which is a collateral of the renal artery. The consequent hyperemia of the adrenals would lead to their hypertrophy, and with this would come an increase in the production of adrenalin which would cause a rise of blood-pressure. Marcuse (*Berl. klin. Woch.*, Bd. xlv, S. 1352, 1909).

Glomerulonephritis was produced experimentally by repeated intravenous injections of *Staphylococcus aureus* toxins in rabbits which had been given a preliminary injection of uranium nitrate. Similar lesions resulted from intravenous use of *B. mucosus capsulatus*. A single large injection caused an acute hemorrhagic nephritis in 6 hours. By reducing the dosage and giving it repeatedly over a long period, the

writer was able to produce the pictures of subacute and chronic nephritis. In the former the most striking change was degeneration of the tubular epithelium. In the latter the kidney under the capsule presented a granular surface and the microscopic picture was that of diffuse chronic nephritis, showing many areas of round-cell infiltration and fibrosis, especially of the glomeruli. Major (Jour. Med. Research, xxxvii, 125, 1917).

The outlines of the individual capillaries are lost, and the glomerular epithelium of the capsule—especially that covering the inside of the capillaries of the tufts—is swelled and opaque. New epithelium appears in most instances of diffuse exudative nephritis, and a restoration of the glomerular function occurs. According to one view, in the productive variety of acute diffuse nephritis, however, certain lesions are more permanent in character from the outset in the glomeruli and stroma, and hence the increased gravity of the disease. Superadded to the usual exudative condition are the following changes: (a) a growth of the cells lining the capsules, such as to form a mass that compresses the tuft, “and leading, finally, to obliteration of the vessels and fibroid glomeruli”; (b) a growth of the connective tissue parallel to, and surrounding, one or more arteries having thickened walls, and forming more or less numerous and regular strips or wedges in the cortex. The new tissue between the tubules is, in the more intensely acute cases, largely cellular; in those of a subacute type it is relatively dense and fibrous.

Pleural, pericardial, and peritoneal dropsy, as well as anasarca, are also found in those dying of acute Bright's disease. Meningitis, cerebral edema, and lobar pneumonia are also sometimes seen *post mortem*.

PROGNOSIS.—A case of ordinary exudative nephritis following exposure to cold and wet runs a course varying from a few days to three or more weeks. There is a steady diminution of the albuminuria, which finally disappears together with the casts, while the daily quantity of lighter urine and the daily excretion of urea increase. The character and intensity of the renal inflammation, and the primary disease or causative conditions largely determine the prognosis. Scarlatinal nephritis gives much less hope of recovery than does nephritis due to exposure to cold after alcoholic excesses. Recovery usually takes place easily after the acute parenchymatous degeneration that accompanies diphtheria, typhoid, and other infectious fevers, as well as pregnancy. In acute yellow atrophy, however, and in yellow fever, cholera, severe phosphoric or mercurial poisoning, death may occur from the intense and widespread necrosis of renal epithelium. The dropsy and albuminuria gradually diminish in favorable cases of ordinary exudative nephritis, while the color of the skin and the quantity of urine and urea increase; so that recovery is established in from three to six weeks. The albumin may persist for some time after the disappearance of the dropsy, and then gradually disappear; rarely, however, in unfavorable cases, albuminuria may continue and the affection become chronic parenchymatous nephritis, even after the dropsy has disappeared.

A small amount of albumin may be present in grave renal lesions, and, on the contrary, a large quantity of albumin may not necessarily mean a fatal prognosis (albuminuria from excessive fatigue). Again, edema may be met with in parenchymatous nephritis, while absent in the interstitial form, in which it appears only

in consequence of cardiac insufficiency. The cardiac and vascular symptoms are of very great importance in forming an opinion about the prognosis. Signs of cardiac debility betoken clearly an approaching danger. Alterations in the retina are of bad prognostic omen; out of 100 cases of albuminuric retinitis Bull followed up 86, 57 died during the first year, 12 during the second, and 17 later. Phenomena of uremic intoxication are not always grave. In acute nephritis the patient may recover after delirium and even convulsions. Headache that resists treatment is a bad indication; if accompanied by vertigo, stupidity, and insomnia, it indicates an approaching explosion of grave symptoms. Dyspnea and asthmatic attacks may last for years, while Cheyne-Stokes respiration appears usually during the last weeks of life, and occasionally during the last months.

Acute nephritis presents a number of serious and often dangerous symptoms. Among these are severe general edema, dropsical effusions into the serous sacs (as hydrothorax), uremia (especially when beginning with cerebral manifestations, as convulsions or coma), and, finally, inflammation of the internal organs, as pneumonitis, pleuritis, pericarditis, peritonitis, and meningitis. Recovery is quite common in cases of marked general dropsy in the absence of uremia. Suppression of the urine, however, if it lasts more than twenty-four or forty-eight hours, is usually a fatal symptom. In those cases, also, in which the nephritis has a productive character, the prognosis is unfavorable, though life may, in some cases, be prolonged for several years.

Study of acute nephritis in children in respect to prognosis in later life in 106 persons who had had acute nephritis before the age of 15, and 50 whose acute nephritis occurred between the ages of 15 and 20. The intervals since the nephritis ranged from sixteen to twenty-three years. The nephritis occurred in connection

with some acute infectious disease in all but 27 in the first group, but in none of the 40 individuals the writer was able to re-examine were there any signs or symptoms suggesting that the kidneys were below par. The same negative findings were observed in most of the 16 relocated and re-examined in the group of 50 older patients. Ernberg (*Nordiskt med. Arkiv*, vol. xlv, No. 2, 1912).

In very severe acute nephritis the renal function during the early stages is much better than the actual state of the kidneys would seem to warrant. This the author ascribes to the stimulation to which the kidneys are subjected at the outset. With the subsidence of the inflammation, however, the renal function tends to fall to a low level. Thus in 1 case an extreme and prolonged impairment in the rate of urea excretion first appeared at a time when the patient was beginning to show marked general improvement. Simultaneously the rate of phenolsulphonephthalein excretion was impaired, but the blood plasma chloride and the chloride threshold returned practically to normal. This is the critical period in acute nephritis; during the resulting prolonged rest of the kidneys great care must be taken not to overstrain the exhausted function. Theophylline probably acts in part by lowering the chloride threshold; the chlorides are thereby allowed to pass out of the blood plasma, and water follows. E. H. Mason (*Arch. Internal Med.*, Feb., 1918).

Studying the prognosis of war nephritis in 50 patients, the authors found almost all cases to show after a period of 3 months a trace of albumin, a few granular and hyaline casts, red blood cells, and pus. The chlorids and urea were about normal. Nocturnal micturition was present in nearly 40 per cent. of the cases. Many still complained of dyspnea, slight headache, and pains across the lower part of the back, and a few developed slight transient return of edema. The patients were usually

well nourished and not anemic, with striking absence of the pale countenance of the ordinary nephritis of civil life. In over half the cases there had been, at the onset acute catarrh of some part of the respiratory passage, most frequently a bronchitis. A. R. Robertson and others (Can. Med. Assoc. Jour., Mar., 1918).

Studying the pathogenesis of war nephritis, the author found that in 40 per cent. of cases the re-establishment of renal function was incomplete and some permanent damage resulted to the general health. Early disappearance of edema is one of the best prognostic signs; its persistence after the second week makes the outlook worse; its presence after the first month indicates that restoration to health will be incomplete. Similarly albuminuria continuing after the end of the third month renders the prognosis as to complete recovery unfavorable. S. C. Dyke (Lancet, Sept. 7, 1918).

TREATMENT.—The first object in the treatment is to relieve the congestion and inflammation, since the renal function is diminished by these conditions; by these means we restore the excretory function. It is, therefore, in order to restore the functional equilibrium by their antiphlogistic influence, that the single or combined use of diaphoretics and cathartics is employed, and not that the skin and bowels should be made to perform the work normally done by the kidneys.

Mercury is not indicated even in the treatment of the nephritis with inherited syphilis. The writer has witnessed hematuria follow mercuric inunctions. Intravenous injection of an **arsphenamine** preparation is now his procedure. The diuresis increases and the general condition improves, but we must not expect rapid improvement or a definite cure. These can be counted on only when treatment is begun in the early stage, while

generally the nephritis is far advanced. V. Hutinel (Paris méd., Jan. 25, 1919).

Absolute rest in a warm bed and in a warm room is of primary importance, and, in order to promote a constant and free action of the sweat-glands, **woolen underwear and blankets** should be used. These measures are of importance both in mild and severe cases.

The **diet** should consist of bland liquid foods only, and the patient should be urged to **drink freely of water** (plain, distilled, or carbonated), **lemonade, skimmed milk, or butter-milk**, all of which are of especial value when hot.

The writer holds that in nephritis a **diet low in protein substances** must be prescribed. The old-fashioned milk diet necessitates the ingestion, if enough nutriment is to be given the patient, of an amount of protein that is considerably above the needs of the normal individual. H. D. Arnold (Trans. Amer. Med. Assoc., June 9, 1910).

In the treatment of war nephritis, besides the usual measures—**rest, warm uniform temperature**, etc.—the **diet** must be regulated by the urea content of the blood and the diastatic ferment in the urine. Salt must not be dropped entirely. **Milk** contains just enough sodium chloride to answer the demands of the tissues without harming the diseased organ. The **Karell course** of dieting serves the purpose, restricting the patient to 800 c.c. (1½ pints) of milk, given at 4-hour intervals during the day for a week. Thirst is allayed by moistening the lips, and hunger by chewing a little toast. After a week of this, 1 egg is allowed, without salt, and other fluids may be substituted as the ordinary diet is gradually resumed, but the total of 800 c.c. (1½ pints) must not be exceeded. The food should always be salt-poor but may include meat, fresh water fish, unsalted butter, cheese, eggs, rice, un-

salted bread, potatoes, peas, beans, fruit, tea, coffee, chocolate, etc. With the diet thus regulated the heart and kidneys are spared to the utmost. Eustachio (*Riforma Medica*, July 14, 1917).

Thin meat-broths may be allowed later in the course of the disease, although a strict milk diet is preferable. If any edema be present, a **salt-free diet** should be the rule, as it has been shown that normal **saline injections** increase the amount of edema.

There is no need to exclude **salt** unless tests show that there is retention of chlorides. Unusual quantities of fluids need not be advised unless there seems to be a tendency to functional paralysis on the part of the kidneys. In this case water is better than drugs to stimulate kidney functioning unless the heart is weak and dilated, in which case the intake of fluids should be restricted. **Venesection** applied to the foot drains the congestion in the renal artery most effectually, but the main reliance is on measures to promote oxidations, and the elaboration of the albuminoid molecule by inhalation of **oxygen** and administration of **iodides** and **alkalines**. Calabrese (*Gaz. degli ospedali*, Oct. 10, 1909).

The writers advocate the advantages of a **milk diet** even when there is no retention of salt and urea; they found that the albuminuria was milder and briefer during scarlet fever when the children were restricted to milk for a time. If the albuminuric nephritis enters a chronic phase, a milk-vegetable diet is necessary, with yolks of eggs and very little meat, moderately salted. With retention of salt in acute nephritis, the children should be restricted to water and little of that for the first few days. The edema is generally rapidly reabsorbed when this is done. Even milk contains enough salt to prolong and intensify the edema during this phase. Salt should not be allowed until certain that the kidneys

are able to eliminate it again. These dietetic measures may be supplemented by diuretics, such as lactose and theobromine or digitalis, if the heart action is weak. Nobécourt and Merklen (*Archives de méd. des enfants*, Sept., 1911).

In view of the occasionally brilliant results that have been obtained; in view of the apparently simple (and correspondingly incomplete and inaccurate) explanations that have been offered, enthusiasm has gone somewhat beyond bounds in regard to **salt restriction** as a therapeutic measure. It is by no means a panacea for all nephritic edemas. With careful selection of types and with methodic regulation and control, salt restriction can probably never do harm and will usually do good; but employed as a routine measure without control, promiscuously, in every case of edema, it will more often disappoint than fulfill the expectations based on it. A. C. Croftan (*Jour. Amer. Med. Assoc.*, Feb. 17, 1912).

The treatment employed by the author in war nephritis is stated by him to have given very gratifying results. At first all patients were kept in **bed** until albumin and casts had disappeared from the urine and there was a fair salt and nitrogen balance; or until there seemed to be no prospect of the albumin and casts disappearing. The **diet** was limited to milk in the very severe cases and in the others it was fixed at 2½ pints (1¼ liters) of milk, 6 ounces (180 Gm.) of bread, 1 ounce (30 Gm.) of rice, 4 ounces (120 Gm.) each, of potatoes and greens, ½ ounce (15 Gm.) of butter and 1 ounce (30 Gm.) of jam, with fruit occasionally. The food was prepared without addition of salt, except in the green vegetables. As improvement progressed, bread was increased, egg yolk added, and later small amounts of fish or chicken permitted. The diet was always given by weight. **Water** was allowed freely. Simple **diaphoretics**, **saline** or other **purgatives**, and **hot air baths** were used when necessary.

Nitroglycerin was given when the blood-pressure was high. **Iron** followed in the later stages for anemia. Where there was deficient secretion of urine, **Fischer's sodium carbonate treatment** was employed, beginning with hourly doses of 0.6 to 1 Gm. (10 to 15 grains) of pure crystalline sodium carbonate in 250 c.c. ($\frac{1}{2}$ pint) of water and increasing the interval between doses when there was free diuresis. **Digitalis** and **caffeine** were also employed, alone, together, or combined with the alkaline treatment when it failed to promote an adequate diuresis. Sensations of great prostration were much relieved by the administration every 4 hours of **epinephrin** in doses of 0.2 to 0.3 c.c. ($3\frac{1}{2}$ to 5 grains). J. M. Clarke (Brit. Med. Jour., Aug. 25, 1917).

In nephritis one should avoid, remove, and combat every condition that favors the abnormal production or accumulation of acids and substances acting like acids in the kidney. In threatened or established cases, one should give **alkali, salts, and water**. The alkali neutralizes the acid present in abnormal amount in the kidney, the salts are indicated because the various changes induced in the kidney colloids by acid are counteracted by adding to such acid any salt, even a neutral salt, and the water is given in order to have more of it present than is necessary to saturate all the body colloids, as otherwise there is no free water left for the secretion of urine. Active administration of **sugar** either by rectum or intravenously is advantageous; carbohydrate starvation is a common cause of acidosis and sugar is very efficient in reducing hydration. Martin Fischer (Penna. Med. Jour., Jan., 1918).

In rare cases in which there is severe pain, local **bloodletting**, by means of leeches or cupping over the loins, may be useful; these measures are seldom needed, however, and a more salutary effect may often be gained by **hot fomentations**.

Bacelli's method of treatment of the early stage of acute nephritis consists of the abstraction of blood from the foot. The treatment is based on the fact that the venous pressure in the kidney is high, and that when the organ is inflamed the pressure is still greater. This leads to degeneration of the renal epithelium. **Bleeding from the foot** tends to cause a diminution of pressure in the inferior vena cava, and hence also in the renal veins. The amount of blood to be withdrawn according to De Rossi, varies in the individual case, but in the adult should not be less than 300 c.c.; in children the amount should be proportionately smaller.

When local depletion, leeching, cupping, and mustard or capsicum plasters are not active enough, in a case of acute hemorrhagic nephritis, the writer advises **venesection** to the extent of 15 or 20 ounces when the function of the kidneys is totally or greatly arrested and the evidences of uremia are pressing. It is not applicable in the nephritis of acute fevers. J. M. Finny (Dublin Jour. of Med. Sci., March, 1908).

Copious **venesection** followed by **transfusion** of normal blood inhibits both qualitatively and quantitatively the characteristic degeneration usually found in the epithelium of the ascending loop of Henle in the kidneys of dogs acutely poisoned by mercuric chloride. Burmeister (Jour. Labor. and Clin. Med., Apr., 1917).

Diminution of the edema and the elimination of urea and other urinary constituents retained in acute nephritis are best attained by exciting a profuse perspiration. The congestion of the kidneys is also relieved by this vicarious action of the skin. The same results may also be accomplished by means of the **hot-air or hot-water bath** and the **hot, wet pack**; in most cases the last method proves effective. It is easily applied by wringing a blanket out of hot water, wrapping the patient in it, and surrounding him, first, with a dry blanket and, finally, with a

rubber cloth. According to the condition, the patient may remain in improvised steam bath until free sweating has continued for an hour or more. Children suffering from scarlatinal nephritis may either be treated thus, or by immersion in hot water for twenty, thirty, or more minutes; the child is then wrapped in warm sheets or blankets, after lightly drying the skin, and warmly covered in bed.

Experimental observations have shown that under ordinary conditions the alterations in volume of the kidney are very considerable, and it was supposed that renal excretion would be favorably influenced by a temporary elimination of these circulatory fluctuations. Observations were made on patients who for an hour and a half were placed in a bath having about the body temperature, and analyses of the urine were made before, during, and after the period of immersion. It was found that the effect of **warm baths** of considerable duration was decidedly beneficial, the excretion of nitrogenous bodies and sodium chloride being greatly augmented, while the total volume of the urine also was considerably increased. The effect on the albumin excreted was less noticeable. The authors consider that the method has practical possibilities and suggest that one or two baths daily of from one to one and one-half hours' duration be tried in suitable cases. More prolonged immersion than this was found to yield less satisfactory results. Strasser and Blumenkranz (Berl. klin. Woch., April 2, 1906).

Careful tests on the effects of **dry heat** on children affected with nephritis showed that local hot applications like the hot electric pad do not give appreciable results. In the absence of special hot-air ovens the writer has employed the following simple method. The child rests in bed with an ice-bag on its head. The bed-clothes are pinned tightly around its neck and lower down kept ele-

vated by wooden arches, forming a species of tent. At the foot of the bed the heat generated by a lamp in a box is admitted through a tin pipe. The duration of the treatment is between half an hour and one and a half hours, the temperature reaching a maximum of 55° C. These treatments are always well borne, with no unpleasant effects. G. B. Allaria (La Ped., June, 1911).

In the presence of nausea in nephritis the writer makes no attempt to give the patient any food whatever, although water is given by rectum in **normal salt solution**—8 ounces every 4 hours by the drop method. If much edema is present, purgation by **magnesium sulphate** and **hot air baths** are employed, but these measures are never prescribed in the absence of edema as they may then be dangerous or even fatal. The hot air bath is, next to bleeding, the best method of reducing high blood-pressure. When nausea ceases, the **diet** is ordered, excluding proteins, especially meats and salt. The diet at this stage consists mainly of milk. Later carbohydrates are added, along with fats, but the proteins are kept low. R. C. Cabot (L. I. Med. Jour., Aug., 1917).

In cases in which a sudden onset or acute suppression occurs, prompt relief often follows **high rectal irrigation** by a gallon of plain water or normal saline, at from 100° to 110° F., repeated every four hours until the function is again established. **Hot air** or **vapor** may also be generated beside the bed and introduced beneath the cradled bedclothing by means of a tin funnel and pipe. The drinking of **hot lemonade** or **soda-water**, or of **water containing spirit of Mindererus**, will stimulate the sweating. Should these measures fail, as in uremia, perspiration may be started by an hypodermic injection of **pilocarpine**, $\frac{1}{8}$ to $\frac{1}{6}$ grain (0.008 to 0.01 Gm.); it will then

continue to pour out upon the application of heat. Serious consequences sometimes attend the use of pilocarpine, and the heart and pulse must always be carefully watched. A safe rule is not to use this drug if any edema of the lungs be present. The sweating should be repeated as often as the patient's strength will permit, until the dropsy disappears.

Hydragogues, as **elaterium**, the **saline cathartics**, and **compound jalap powder**, are useful as adjuvant measures. The extract of elaterium ($\frac{1}{8}$ to $\frac{1}{4}$ grain—0.01 to 0.016 Gm.) is prompt in action, and **magnesium or sodium sulphate** (1 dram—4 Gm.) given in hot concentrated solution every hour, or a **calomel** purge, may also be recommended. In extreme cases of dropsy it may be necessary to relieve the tension and distress by the use of a small **trocar** and **cannula**, with a **drainage-tube** (Southey) attached to the latter after the trocar is withdrawn, or by multiple punctures. If either hydrothorax, hydropericardium, or ascites assumes serious features, **aspirations** will become necessary. To the diaphoretic treatment may be added $\frac{1}{2}$ -ounce (0.032 Gm.) doses of the **spirit of Mindererus in water**. This, combined with **aconite**, aids in controlling the fever that may be present and in preventing the vasoconstriction that is often premonitory of uremic symptoms.

The writer tried Wright's **vaccine** technique in colon-bacillus nephritis and pyelitis. Though he undertook it with much skepticism, he has become convinced of its great value. In 4 of the 12 patients thus treated there was prompt recovery after failure of all other measures. It should always be tried in all cases rebellious

to other methods. The reaction, both general and local, was surprisingly mild. Rovsing (*Hospitalstidende*, May 12, 1909).

In the treatment of infectious nephritis the specific drug indicated should be used without much regard for its action on the kidney. In syphilitics it is hard to know whether the nephritis is of syphilitic nature or not, but in the presence of a negative Wassermann finding mercury should be avoided. **Diphtheria antitoxin** is useful in the nephritis that accompanies diphtheria. In streptococcus or staphylococcus nephritis, **vaccines** should be used according to Wright's technique; this may also prove useful in nephritis from the diplococcus, etc. In acute nephritis with fever, drugs to reduce the fever should be avoided. The febrile process is treated by graduated **hydrotherapy**. Arcangeli (*Policlinico*, Med. Section, April, 1910).

In the nephritis of childhood the writer advises as follows: 1. For two days prohibit all food, giving only 500 or 600 Gm. (1 pint or 20 ounces) of water, sweetened with table- or milk- sugar, daily. Then give 500 Gm. of milk and same amount of water. When condition becomes sub-acute, add carbohydrates, as preparations of flour, potatoes, etc. Add sugar to milk; when distasteful, dilute milk with Vichy, or give it alternately raw and boiled. Where **milk diet** not tolerated or results poor, try salt-free diet, omitting proteids and limiting milk to small amounts. Later, if no complications, lean ham, fresh pork, lamb, and chicken may be given. Milk should not be taken with meals. 2. **Rest in bed** and avoidance of exposure. 3. Stimulate skin by **general rubbings**, **gentle massage**, and **tepid baths**. **Hot pack**. 4. **Dry cupping**, **wet cupping**, or **leeching** over triangle of Petit. 5. **Systematic disinfection** of mouth, nasal fossæ, and pharynx, and treatment of skin lesions as possible portals of infection. Where excretory insufficiency appears: 6. **Hot-air** or **vapor baths**. 7.

Drastic purgative, followed by laxative. When signs of intoxication appear: 8. **Theobromine**, 0.5 Gm., at most 0.75 Gm. ($7\frac{1}{2}$ or $11\frac{1}{2}$ grains) at a dose in child of 10 to 13 years. **Powdered squill, digitalis, and scammony**, 0.025 Gm. ($\frac{1}{8}$ grain) of each in a pill, given two or three times daily. If circulation weakens, **digitalin** or **infusion of digitalis**. **Convallaria** or **convallamarin**. **Sparteine** in the dose of 0.04 or 0.05 Gm. ($\frac{3}{4}$ or $\frac{1}{2}$ grain) in the twenty-four hours. Hutinel (Bull. méd., Feb. 16, 1910).

In proportion to the severity and duration of an attack of acute nephritis will we find the blood impaired in its integrity, and a condition of anemia and debility; hence, tonics are to be considered and have an important place in the therapeutics of this disease. All the standard authorities commend the use of **iron** in some form, the preference by many being for the old tincture of the chloride; but for many years the well-known and somewhat ancient **Basham's mixture** has been the writer's personal preference, giving it in full doses every four to six hours, proportionate to the age of the patient, and not commencing its administration until the symptoms of nephritis begin to decline. D. J. Roberts (Southern Pract., April, 1910).

The writer treats nephritis occurring with secondary syphilis by injections of mercuric cyanide, giving daily $\frac{1}{2}$ c.c. of the following solution:—

R. *Mercuric cyanide* 2 Gm. (31 grs.).
Sodium citrate. 0.05 Gm. ($\frac{3}{4}$ gr.).
Sodium chloride 0.35 Gm. ($5\frac{1}{2}$ grs.).
Distilled water. 100 Gm. ($3\frac{1}{4}$ oz.).
 Ft. solutio.

Jeanselme (Jour. de méd. de Paris; N. Y. Med. Jour., June 11, 1910).

Acute nephritis may be caused by any acute disease of childhood, and we should be on our guard in all acute infections just as we are in scarlet fever. Case of nephritis in which there was an increased amount

of cerebrospinal fluid, a **lumbar puncture** gave apparent benefit. In treatment the writer speaks of 4 cardinal points: 1. Care of the skin, that is, keeping the child warmly clad and in bed. 2. Elimination from the skin and bowels, and 2 to 4 evacuations in twenty-four hours with **Rochelle salts**. 3. Diet; during the acute stage, the more nearly the patient can be kept on a milk diet the better the result. 4. The treatment of complications. Headaches and muscular twitchings are valuable danger signals, and usually precede uremic convulsions. The most important remedy for convulsions is **morphine** given hypodermically. Acute dilatation of the heart, as indicated by an increased area of dullness and the character of the pulse, demands prompt attention, with **ice-bags** or **digitalis** when the pulse is rapid and the child is lying quietly. After apparent recovery the child should remain under the observation of the physician for two years or longer. McClanahan (Pediatrics, Jan., 1912).

In 2 cases of acute and 1 of chronic nephritis remarkable benefit was obtained with **adrenalin**. To a child nearly 5, the writer gave 16 drops a day of the 1:1000 solution, 4 drops at 4-hour intervals. The adults were given 40 drops a day, 8 at a time. Ercolani had called attention in 1910 to the benefit from adrenalin by mouth in nephritis. Borelli (Polislinico, Apr. 30, 1916).

Mercury does not seem advisable in treatment of the nephritis with inherited syphilis. The writer has even witnessed hematuria follow mercuric inunctions, and consequently he refrains from mercury in treatment of nephritis with suspected inherited syphilis. Intravenous injection of an **arsphenamin** preparation is now his procedure. The diuresis increases and the general condition improves, but we must not expect rapid improvement or a definite cure. These can be counted on only when treatment is begun in the early stage, while generally the nephritis is far

advanced and cicatricial tissue has formed at some points. V. Hutinel (Paris méd., Jan. 25, 1919).

If the uremic convulsions do not promptly yield to diaphoresis and catharsis, **venesection** must be resorted to, the withdrawal of as much as a pint or two of blood often saving life. Occasionally **inhalations of chloroform** are needed to subdue the violent convulsive seizures, as in eclampsia. Their recurrence may be prevented by the use of **rectal injections of potassium bromide** (1 dram—4 Gm.) and chloral ($\frac{1}{2}$ dram—2 Gm.).

Contraction of the arteries with increased tension and beginning muscular twitchings requires the use of **chloral hydrate**, **nitroglycerin**, and, possibly, **morphine**.

Nausea and vomiting may be held in control by minute doses of **cocaine**, **cracked ice**, **dilute hydrocyanic** or **hydrochloric acid**, **bismuth**, or by the addition of **soda-** or **lime-water** to the **milk**.

There is little advantage in diuretics other than the simple diluent drinks already mentioned, at least early in the course of the disease. Later, **potassium bitartrate** or **acetate**, **sodium benzoate**, as adjuvants to the water, and **stimulants** to relieve cardiac depression, or **caffeine citrate** and the **infusion of digitalis**, may be given, well diluted.

Renal organotherapy was applied by the writer in a case of a robust young man who, in the second or third week of an attack of influenza, suddenly developed pulmonary edema. The right kidney and ureter were found to be extremely tender, and the left slightly so. The symptoms of acute nephritis becoming more threatening with a tendency to coma, the patient was given a subcutaneous injection of 10 c.c. of **serum from the**

renal vein of a goat. Seventeen hours later copious diuresis set in and the alarming symptoms subsided. The injection was repeated the next day, and organotherapy thereafter continued with **kidney extract**. This being suspended after 3 days, next day there was another, but less severe, attack of pulmonary edema. Recovery occurred. The dyspnea was ascribed to toxic weakness of the heart, and **citrated caffeine** given by the mouth or subcutaneously, was promptly effectual. Gil y Ortega (Siglo Medico, Sept. 8, 1917).

Care must be taken during convalescence that the patient be not exposed to cold. The diet must not be changed to solids either too suddenly or too rapidly, and particularly does this rule hold in the matter of meats. Milk should form the mainstay of the dietary, and light, watery, vegetables, fruits, and cereals may be gradually added. The anemia will indicate the ferruginous tonics.

Carefully regulated habits in regard to dress, exercise, and diet, and a change to a warmer, drier, and more equable **climate**, are necessary in cases that are convalescent from the very serious forms of nephritis, in which the renal parenchyma, by the persistence, at intervals, of a slight albuminuria, is shown to have been somewhat damaged.

Puncture of the kidney has recently been recommended.

A boy aged 12 had an ordinary case of scarlet fever, but twenty days after the onset of the fever he was taken with very severe vomiting; twelve hours later he had a hard convulsion, and passed a small amount of bloody urine heavily loaded with albumin. The boy was put in hot packs with hot linseed poultices over the kidneys, pilocarpine and digitalin given hypodermically. This treatment was followed four successive days with no apparent benefit. On the morning of the fifth day there was complete loss of vision and hear-

ing, and a few hours later the patient lapsed into unconsciousness, with complete suppression of urine.

Under ether anesthesia both kidneys were **decapsulated** at the same time. They were found to be as large as an adult's kidneys, very tense and congested. On removal of the capsule the blood fairly boiled from the kidney surface, showing the very high pressure it was under.

The first twenty-four hours after operation the apparently functionless kidneys secreted 24 ounces of urine. On the third day sight and hearing began to return, and at the end of the first week both were normal. The kidneys were also secreting the normal amount of urine. The boy left the hospital on the eighteenth day, able to walk, and feeling normal in every way. G. F. Harding (Jour. Amer. Med. Assoc., July 10, 1909).

The treatment with **blood-serum** from the renal vein is similar to the organotherapeutic treatment; the indications for both treatments are the same. Renal insufficiency in its several degrees and from its many causes may always be treated with this serum, although the success is not sure; the effect is prompter and more pronounced in the milder kidney affection; it produces a more or less severe change of the epithelium of the kidney. Although the same precautions should be observed in serum treatment as in organotherapy, the serum treatment is easier to be applied and more readily tolerated by the patients. The influence of the serum upon the kidney itself and the urine is readily observed; under the influence of the injections the diuresis increased to 6, 8, or even 10 liters during twenty-four hours; certain modifications of the symptoms could be seen, such as the disappearance of edema and dyspnea, headache and insomnia were relieved, etc. Spillmann and Parisot (Presse méd., Oct. 27, 1909).

Nephrotomy resorted to in 3 cases of acute hematogenous nephritis. Recovery was prompt and complete;

moreover, functional tests of the kidneys nearly a year later showed practically complete recuperation. The chief danger of conservative surgical treatment is that the bacteriuria is left and it may prove a source of infection. In 1 of the writer's cases the other kidney became involved and presented a transient syndrome indicating brief mild infection. Baum (Mitt. a. d. Grenzgebieten der Med. u. Chir., Bd. xxi, Nu. 5, 1910).

Ten cases in which the writer operated on the kidney to relieve intense pain in the course of nephritis, with or without pus. The operation arrested the pain permanently in all the cases, although the later after-history of one of them is not known. V. Rochet (Lyon Chir., Sept., 1911).

When acute nephritis persists and anuria, uremia, or miliary abscesses develop, operative intervention is indicated. **Nephrotomy** with prolonged drainage is the preferable technique. The anuria of subacute nephritis is otherwise almost inevitably fatal. The writers found 13 cases on record of operative treatment of acute nephritis; 5 of 14 patients recovered. Worms and Hamant (Annales des mal. des org. genito-urin., Nov. 1, 1911).

Hematuria, renal colic, and anuria which are dependent on inflammatory processes in the kidney and are resistant to any other form of treatment may be brought to a standstill, or caused to disappear, by the relatively easy operation of **decapsulation**, but Bright's disease is never influenced by this procedure. Lichtenstern (Med. Klinik, July 30, 1911).

The writer recommends serum of blood drawn from the renal vein of the goat after trying it in 4 cases in which this **serotherapy** was systematically applied. The results encourage its further use in acute exacerbations of chronic nephritis, in all infectious diseases with threatening uremia, in cases of excessive arterial tension supposedly of renal origin, and whenever uremia is installed, regardless of its origin. The

writer administered without by-effects from 10 to 110 c.c. (162 minims to 3½ ounces) as the daily dose, but for fear of accidents from serum sickness never gave over 20, 30, or 40 c.c. (¾, 1, 1½ ounces) at a time. In the first case the interstitial nephritis was in the terminal stage; but under the serotherapy 1500 c.c. (50 ounces) of urine were voided and 3 per thousand chlorides, the headache and dyspnea subsided, and the blood-pressure dropped,—effects which months of other treatment and dieting had not been able to obtain. M. T. M. Bisso (*Semana Medica*, Buenos Aires, Feb. 15, 1912).

CHRONIC EXUDATIVE NEPHRITIS, or CHRONIC PARENCHYMATOUS NEPHRITIS, sometimes termed **Chronic Bright's Disease**; **Chronic Diffuse Nephritis with Exudation**; **Chronic Tubal and Chronic Desquamative Nephritis**; **Large White Kidney**; **Secondary or Fatty and Contracted Kidney**.

DEFINITION.—A chronic diffuse inflammation of the kidneys, attended with epithelial degeneration, exudation from the blood-vessels, and permanent connective-tissue changes in the renal stroma. This is one of two varieties of chronic Bright's disease, and is identical with Delafield's chronic productive (or diffuse) nephritis with exudation.

There is only one nephritis, the interstitial, all other so-called inflammations representing parenchymatous degenerations. Thus, parenchymatous nephritis must be interstitial nephritis plus parenchymatous degeneration. The authors have performed different sets of experiments intended to illuminate the nature of the nephropathies. The kidneys were extirpated from one rabbit, and after it had in consequence become uremic its blood was transfused into a healthy rabbit. Thereupon there developed in the latter evidences of intense functional activity of the kid-

neys, as shown by the degree of hyperemia and amount of granulation in the renal cells. It was evident that the latter underwent a certain amount of degeneration from the formation of nephrolysins. The degeneration was attended by extravasation of blood. Again, as a result of innumerable punctures with a cautery needle the kidneys could be made to undergo contraction. The islets of intact renal tissue could be seen in the act of doing compensatory work. In this sort of kidney there was no notable degeneration of the parenchyma as a result of the overwork, such as was evident in the first series of experiments. In a third set of researches it was sought to determine whether or not the constant excretion by the kidneys of foreign albumin could set up nephritis. The results when egg albumin was absorbed from the peritoneum and then eliminated by the kidneys were negative throughout. Hirsch and Maschke (*Jour. Amer. Med. Assoc.*, from *Berl. klin. Woch.*, Jan. 22, 1912).

SYMPTOMS.—The symptoms of an acute parenchymatous nephritis may persist in a lesser degree until the condition becomes a chronic one; particularly is this true of the albuminuria, the anemia, and the dropsy. As a rule, however, the disease develops slowly and gradually, and in a subacute manner, although there is seldom an early indication of renal derangement. There may be merely a loss of appetite, attacks of indigestion, nausea, headache, dullness, perhaps some pallor, and a general impairment of health and strength. The complexion then takes on a blanched appearance, and there is soon puffiness of the eyelids, or swelling of the feet or ankles, or both. There is a gradual extension of the edema up the legs, and as the day grows it becomes worse; on rising in the morning it may have entirely disappeared. In

the majority of cases the quantity of urine is diminished. In the later stages of the disease, however, it may be nearly or quite normal, and in protracted cases of pale contracted kidney, or when absorption of the dropsical effusion is in progress, it may even be slightly increased.

An acute nephritis supervening upon the chronic condition may now cause a very scanty or suppressed secretion of urine. In cases of scanty urine the specific gravity is, of course, increased, and *vice versâ*. Albuminuria is often present to a decided degree. The albumin may constitute as much as from one-fourth to three-fourths of the urine in volume, or from 1 to 3 per cent. by weight daily.

The quantity of urea is much diminished. The urine contains an abundant sediment, consisting of urates, casts, red and white blood-corpuscles, epithelial cells, granular *débris*, and fatty granular cells, and is in color turbid and sometimes smoky yellow. There are tube-casts of different varieties, the narrow or broad hyaline, fatty granular, and epithelial casts being most commonly noted.

Casts may be absent from a certain number of cases which otherwise are typical cases of nephritis, being destroyed by lysis resulting from the action of the *Bacillus coli*. Again, albuminuria is by no means always indicative of permanent disease, unless considerable in amount and more or less constant in occurrence. The nature of the accompanying tube-casts must not be too greatly relied on to determine the seriousness of the renal lesion. Even the definite hyaline cast, as distinguished from the insignificant cylindroids of the mildest grades of renal irritation, is so frequent in arteriosclerosis, cardiac or hepatic disease, and in gouty conditions, that its significance is comparatively trivial without general corroborative clinical symptoms.

According to Schütgen, the leucocytes occurring in the urine in Bright's disease are lymphocytes. In certain cases the presence of lymphocytes alone in the sediment is capable of affording a differentiation between Bright's disease and renal abscess or pyelonephritis.

The general rules for the urinary findings are as follows: *Temporary congestion, active or passive*: Urine scanty, high-colored, smoky, or dark; specific gravity high; albumin present in small amounts; a few erythrocytes and leucocytes present; a few hyaline and occasionally granular casts.

Acute parenchymatous nephritis: Urine scanty to even anuria, high-colored, smoky, brown, or almost black; specific gravity high; albumin present in large amounts to complete consolidation. Red and white blood-cells fairly abundant; hyaline, pale and dark granular blood-casts, and occasionally epithelial and pus casts. With the latter present, the possibility of the acute interstitial form of nephritis should be remembered.

Chronic parenchymatous nephritis: Urine varies in amount from a little subnormal or normal to a considerable increase; color pale or normal; specific gravity usually lowered, urea diminished; albumin reaction well marked; renal cells; hyaline, granular, epithelial, waxy, and rarely oil casts may be found. This form of nephritis is subject to acute exacerbations when the findings approximate those of the acute form.

Interstitial nephritis: Urine increased in amount, pale; specific gravity often very low; urea low; albumin slight in amount and infrequently apparently absent; casts few, usually wide hyaline, occasionally granular, and rarely waxy. J. H. J. Upham (Lancet-Clinic, Sept. 8, 1906).

The author approves of Mallory's division of nephritis into the tubular, glomerular, and vascular types. (1) Tubular nephritis is rarely seen. It is almost always acute and due to a poison, especially corrosive subli-

mate. (2) In acute glomerular nephritis all parts of the kidneys are affected but the glomeruli far more than the tubules and vessels. The condition is usually part of a general streptococcus infection and is to be feared in every severe case of tonsillitis. (3) Vascular nephritis is the ordinary nephritis of old people, *i.e.*, arteriosclerosis, producing a scarred and broken-down kidney. There is always general arteriosclerosis as well, but the renal involvement may be altogether out of proportion to the involvement of the arteries elsewhere. Chronic interstitial nephritis is the end result of all types of nephritis provided they last long enough, and is not a special variety, and does not cause a peculiar clinical type identifiable by the urinary findings or in any other way. In well-marked nephritis with a low blood-pressure, amyloid degeneration may be suspected.

Of the albuminurias which are not nephritis, the only one of importance is the so-called "albuminuria of adolescence," sometimes called cyclic or orthostatic albuminuria. Lee examining freshmen entering Harvard, found that about 10 per cent. had a well-marked albuminuria, only rarely with a genuine nephritis. The severe case of tubular nephritis depends for a diagnosis mostly on a knowledge of the cause. The urine is not characteristic in itself. It is impossible to distinguish the urine of mild tubular nephritis from the urine of passive congestion of the kidney, of anemic states or febrile states, or of many other conditions in which one finds albumin and casts in small quantities.

Acute glomerular nephritis, in the author's experience, with post-mortem work, proved to be one of the most difficult of diagnosis to make. Only in a small minority of cases are there characteristic manifestations, *viz.*, (a) uremic symptoms, such as headache, vomiting, convulsions, coma; (b) general edema; (c) high blood-pressure, and (d) the urine in which the most characteristic thing is

the presence of blood. There may be considerable diminution in the amount of urine, but not such extreme diminutions as in toxic tubular nephritis. Cases diagnosed as acute glomerular nephritis were generally found to be chronic at autopsy.

In the subacute or chronic cases there is blood in the sediment, but as they go on the blood diminishes and the fat increases. Later, the casts diminish until in the later years it may be impossible to find any at all. If one finds a large number of casts in the urine one can be fairly sure that the kidney is not badly damaged. Casts are of no value in the diagnosis of renal disease because they are found so often in diseases which are not nephritis, because they are so often lacking in nephritis, and also because we have now so many tests of the kidney function which are superior in value to the examination for casts.

One of the most valuable signs of chronic nephritis is the measurement of the day and night urine. The night amount may be twice the day amount, or even more. The author always instructs patients to collect separately the day urine, 7 A.M. to 7 P.M., and the night urine 7 P.M. to 7 A.M., to measure them, then to mix them and bring him a mixed specimen of the total amount. With the increased amount at night goes a progressive fall in the specific gravity. Another point is the fixation of the specific gravity, *viz.*, if one gives the patient abundant water one cannot dilute his urine and when water is withheld one cannot concentrate his urine. In making the test, one has him pass his urine, as far as possible, every 2 hours during the day time and as frequently as he conveniently can during the night. With this goes, in most cases, a retention of nitrogen, to be tested best by the Folin tests in the blood. The retained nitrogen in normal people is somewhere between 25 and 40 milligrams per 100 c.c., and in the nephritis cases it runs up to 100, 150 and

even 200. This retention is a threat of impending uremia.

A diagnosis of acute uremia is often wrong because the condition is apt to cause coma and the urine in any case of coma is practically certain to contain albumin and casts in considerable amount. One should never make a diagnosis of acute uremia without evidence in the heart, subcutaneous tissues (edema), and history.

Chronic vascular nephritis is a slow gradual process. The specific gravity of the urine is not so low, the nocturnal polyuria not so great, the specific gravity not so fixed, but in other respects it is almost impossible to distinguish it from chronic glomerular nephritis. Age is the chief differentiating point. Another point is that anemia is not nearly so prone to develop in chronic vascular nephritis. The retinae have not served the author well as a means of differential diagnosis. Urea determinations depend primarily on the food. A much more accurate test of renal function than the urea output is the phthalein test.

If a nephritis is acute and if it is diagnosable at all, there are perfectly diagnosable signs in the urine. If chronic, it will show in the heart in practically every case and in the blood-pressure. R. C. Cabot (*Med. Standard*, Oct., 1917).

Absence of albuminuria must not be taken as definitely excluding chronic nephritis where the symptoms of arterial pressure favor such a diagnosis. Resort must then be had to other methods, such as Ambard's coefficient, and great care taken in observing the patient. Urine containing but a trace of albumin not infrequently proves misleading, the renal disease turning out to be more grave than one has been led to believe it.

Whenever the amount of albumin passed diminishes in the course of nephritis, the improvement should be estimated rather from the patient's general appearance, the symptoms,

the blood-pressure, and the Ambard coefficient or blood urea estimation, the albumin, as a matter of fact, constituting no measure of the functional efficiency of the kidneys. H. Baril (*L'Union méd. du Can.*, Apr., 1918).

The edema is prominent and persistent, gradually extending all over the body; thus pitting may be obtained on pressure on the limbs, chest, abdomen, and back.

The loose subcutaneous tissues, as of the penis, scrotum, and eyelids, are especially distended. Only in chronic hemorrhagic nephritis may the edema be absent or very slight. Chronic exudative nephritis, especially with large white kidney, shows a pasty, pallid skin and anasarca as its most distinguishing characteristics. For several months the dropsy may be of moderate degree and almost stationary; it then grows worse insidiously, in spite of all efforts at treatment, and death ensues in a month or two.

In cases of chronic parenchymatous nephritis, in which the kidneys are compensating fully, the quantity of water, nitrogen, and chlorides remains normal in both plasma and red blood-cells. Even with edema the solids of the blood may be normal, but the plasma is diluted and is relatively increased as compared with the red blood-cells. Hydremia with dilution of the plasma affects cases without edema, and depends on the increased amount of plasma as compared with the red blood-cells. Hydremia with dilution of the plasma is found particularly in edematous patients and is due principally to the retention of water. In the course of chronic parenchymatous nephritis the writer usually finds the sodium chloride practically normal in the plasma and in the red blood-cells—the relative amounts of this salt in the corpuscles and plasma being as 1 to 2 in health; but this ratio may be al-

tered to 1 to 5. Halpern (*Deut. Arch. f. klin. Med.*, Bd. xciii, S. 585, 1908).

Case of chronic parenchymatous nephritis in which there was a decided tendency to the formation of fibrin in the blood, and the constant escape of white blood-corpuscles in the urine. Allard Memminger (*St. Louis Med. Rev.*, Sept., 1911).

There may be present in serious cases dropsy of the serous sacs, with its accompanying distressing symptoms; edema of the larynx and lungs may then supervene, causing sudden death. Dyspnea may occur, both toxic and nervous, as well as mechanical or cardiac, in origin. On lying down, cardiac dyspnea, due to failure of the heart's action and seen in many instances, is aggravated, as a rule.

It may be provoked by vasoconstriction, and is, in such cases, a signal of uremia.

With these conditions may be associated catarrhal bronchitis, with cough and expectoration.

There is frequently a moderate degree of cardiac hypertrophy of the left ventricle; later there are dilatation and weakness of both ventricles. There is an accentuation of the aortic second sound and an increase of the pulse-tension.

Headache, vertigo, sleeplessness, nausea and vomiting, diarrhea, and stupor, coma, or delirium may all develop and form the symptoms of a uremic condition.

These symptoms, as a rule, precede a fatal termination. The convulsions that are common to chronic nephritis without exudation do not appear, however. In quite a large number of cases albuminuric neuroretinitis occurs, and is evidenced by dimness of vision and field-defects. In certain cases of marked edematous distention the skin

of the legs becomes subject to a red eczematous eruption. The temperature is practically normal in the absence of such complicating inflammations as pericarditis, endocarditis, pneumonitis, and ulcerative colitis, all of which are rare conditions.

A clinical sign observed in disease of the kidney at any early stage: a regular vibratory closure of the eyelids, occurring usually in the beginning of the disease. The vibration affects usually the upper lids, most frequently one lid; rarely it occurs in the lower lids. If it occurs at the external commissura, the entire eye will share in the movement. The duration of the attacks is thirty minutes and sometimes more. The attacks may often be repeated for a number of days and then cease. There is a marked variability in different individuals with respect to the appearance of this symptom, which does not show itself infallibly in all cases affected or threatened with nephritis. G. Ullman (*C.-r. de l'Acad. des Sci.*, Sept. 11, 1905).

Series of 31 cases of renal hemorrhage occurring in chronic interstitial nephritis, selected from 2229 cases of granular kidney, a frequency of 1 in 72. It was at first thought that hemorrhage was always a late complication, but of the cases here reported the average age was 26.2 years, the youngest being 8 years and the oldest 64 years. In 21 cases there were no signs of disease other than the state of the urine, hematuria being the first indication of a chronic nephritis and calling attention to it at an early stage of the disease. In only 6 of the 31 cases were any changes found in the fundi of the eyes. Sex had little or no influence in the causation of hematuria, 29 cases being in men and 16 in women, —the usual ratio in granular kidney. McNab (*Lancet*, April 11, 1908).

Some years ago Barker and Hanes noted that out of 28 cases, 2 of the chronic parenchymatous and 26 of the chronic interstitial form, both of

the former class and 12 of the latter presented exophthalmos of varying degrees. Each of the 12 also showed von Graefe's and Stellwag's signs, while 7 presented in addition the sign of Moebius. In 5 cases the exophthalmos seemed more marked on one or the other side. In none of the cases was the thyroid gland visible or palpable. Though most marked in the advanced cases suffering from serious toxemia, the exophthalmos was distinctly visible in those less advanced, with fairly compensated hearts and without distinct uremic manifestations. In 5 of the 12 cases with exophthalmos albuminuric retinitis was present, and in 6 cases arteriosclerotic changes in the retinal vessels with hemorrhages were observed. In no case was tachycardia a prominent symptom.

The most probable explanation of the exophthalmos and associated signs in chronic nephritis is, according to the writer, an irritation of the cervical sympathetic fibers by toxins floating in the blood-stream the result of chronic renal insufficiency. Aran and Kaufman demonstrated that exophthalmos resulted from stimulation of Müller's non-striated muscle in the eyelids. Landström more recently found that these smooth muscle-fibers formed a narrow cuff encircling the anterior portion of the orbit. Its attachments are so disposed that, in contracting, the muscle tends to draw the eye forward, producing exophthalmos; to separate the lids, creating Stellwag's sign, and to cause the axes of the eyes to diverge, producing Moebius's sign.

While exophthalmos accompanies Graves's disease, paralysis agitans, retrobulbar growths, brain tumor, sinus thrombosis, or hydrocephalus, and prominent eyes occur in cases of myopia and tuberculosis, its presence should always lead to a careful consideration, in the diagnosis, of chronic nephritis, particularly if it is unaccompanied by thyroidal enlargement or marked tachycardia. H. C. Gor-

dinier (N. Y. State Jour. of Med., Aug., 1911).

Neuroretinitis albuminurica is seen but seldom in acute, diffuse glomerulo-nephritis, and in about one-half the cases of malignant renal sclerosis and of chronic diffuse glomerulo-nephritis in the stage of insufficiency. It is, in fact, related to disease of the glomeruli. Its absence is of value in differentiating between benign and malignant sclerosis. When it is present the patient cannot live over 2 years. The amaurosis of eclampsia is a manifestation of eclamptic uremia, in which the eye grounds are normal save for occasional papillary edema. The prognosis is good, and improvement usually follows lumbar puncture. The so-called pseudoureemic ocular disturbances are seen only in renal sclerosis. They are usually very fugacious, and are probably dependent on arteriosclerosis and spasm of the cerebral arteries. Machwitz and Rosenberg (Münch. med. Woch., Oct. 31, 1916).

The index of urea excretion derived from Ambard's laws by McLean gives much more information as to the degree of renal impairment and the prognosis than does the blood urea determination alone. Chronic nephritis with normal blood-pressure may or may not have sufficient renal impairment to alter the relation which normally exists between the blood urea concentration and the urea excretion, that is, it may have a normal or a low index of urea excretion. In general, the phenolsulphonephthalein test parallels the index of urea excretion; but there are marked exceptions to this rule in which the phenolsulphonephthalein test apparently gives an erroneous idea of the degree of renal impairment. R. L. I. Smith (Jour. Amer. Med. Assoc., Jan. 27, 1917).

A close parallelism exists among the new tests for determining renal insufficiency and early nephritis. For general applicability the author recommends first the determination of the

fluid intake and output with special reference to the fixation of quantity and specific gravity and to nocturnal polyuria. If any irregularities appear from this procedure, they can then be supplemented by the more difficult tests. The phenolsulphone-phthalein test is always necessary. These procedures can be applied by any physician. Of the more complicated blood tests, the estimation in order are the urea nitrogen and the non-protein nitrogen retention after proper consideration of the proteid intake. The late appearance of creatinin would appear to give this test doubtful value as a diagnostic procedure, since by this time the other tests are equally instructive and the subjective symptoms themselves hardly admit of an incorrect diagnosis. The point, however, as to its prognostic value, is well taken. When all the foregoing tests have been applied, Ambard's constant is no additional labor. C. W. Dowden (Ky. Med. Jour., May 1, 1917).

Extrarenal factors such as severe anemia or cardiac decompensation influence renal function profoundly. Under such conditions renal function tests may indicate advanced nephritis and yet the kidney itself be structurally sound. If renal function is depressed, one must determine by thorough examination whether it comes from a pathological kidney or from extrarenal disturbance before drawing conclusions. Improvement of renal function accompanying improvement of extrarenal conditions is an indication of a structurally sound kidney.

If renal function is poor in the absence of serious disturbance in other organs, the probability of improvement in renal function is slight except in acute nephritis. In chronic nephritis prognosis can be determined from renal function with greater success than in extensive extrarenal disturbances. Where progression of the disease seems to be by sudden exacerbations the prognosis must be more guarded than where progression is steady.

In hospital practice the author makes use of four tests: (1) phenol-sulphonephthalein elimination; (2) blood urea and rate of urea excretion; (3) specific gravity, sodium chloride and nitrogen content of the urine collected in 2-hour portions during the day, with special diet; (4) the amount of diuresis produced by such a diuretic as theophylline. When blood urea is not increased considerably, the kidney can be excluded as a cause of coma or other serious symptoms and prognosis depends on existing extrarenal disturbances. In mild cases the 2-hour test is particularly useful. The patient is put on a standardized diet for 2 days and on the third day the special meals and the urinary collections are made. During the day, blood and urine are taken for the Ambard coefficient or the McLean index. If phthalein excretion is 35 to 45 per cent., moderate renal disturbance is present. If edema is marked and in combination with digitalis, theophylline produces prompt diuresis, renal function is good; if not, it is poor and the prognosis worse. If phthalein elimination is below 35 per cent., renal function is poor and in patients without cardiac decompensation this indicates usually severe renal lesions. Ambard's coefficient usually parallels phthalein excretion. After phthalein excretion becomes low, determinations of blood urea are of value for as they continue to rise they indicate a nearer approach to uremia. H. A. Christian (Penna. Med. Jour., xxi, 233, 1918).

Chronic exudative nephritis may either continue from bad to worse, and death may end all in a year or two; or anemia, albuminuria, and dropsy may appear in a person that has, for years previously, enjoyed apparently good health. After a first attack a second proves fatal within a few months. On the other hand, certain cases may show a slight pallor, a slightly diminished quantity of urine of high specific

gravity, and containing albumin, and yet may complain of no inconvenience for years. Decided attacks may then occur at intervals, during which the dropsy, dyspnea, etc., may be absent, although a certain amount of albuminuria persists; these attacks last for several months. The average duration of the disease varies from one and one-half to three years.

ETIOLOGY.—Chronic nephritis with exudation may either follow acute diffuse nephritis (as of scarlet fever or pregnancy), or simple chronic congestion and chronic degeneration of the kidneys. It arises insidiously more frequently, however, and without any previous acute manifestation. Males are more subject to this form of chronic Bright's disease than females. Cases occurring in children are usually preceded more or less recently by scarlatinal nephritis.

Young adults are more commonly affected with the usual form, developing subacutely. Beer-drinkers, and those who are accustomed to using malt and alcoholic intoxicants, seem especially liable to the disease. Even in cases where other manifestations are absent, it is not improbable that, in the insidious cases, some toxic or infectious agency may act slowly and persistently, and be the cause of the nephritis.

The disease has been observed in certain individuals living in malarial regions,*and persons working under an exposure to cold and wet, or living in humid, marshy districts, seem more liable to the renal malady than those who are more carefully shielded from such influences.

This so-called "parenchymatous" form of chronic Bright's disease may find its cause in tuberculosis, syphilis, or chronic suppuration, and in such cases it is usu-

ally combined with amyloid disease (waxy degeneration).

As yet too little work has been done for the studies in experimental nephritis to throw much light on the etiology and treatment of nephritis. Injections of various irritants has resulted in a certain number of cases in the production of lesions fairly analogous to the chronic renal lesions that we find in man. In animals, however, the remarkable recuperative power of the kidney makes the production of chronic lesions very difficult. Christian (*Jour. Amer. Med. Assoc.*, Nov. 27, 1909).

The loss of function in chronic nephritis is made distinctly more dangerous by the thoughtless use of so-called diuretics. Casts and albumin do not mean the death warrant, and their presence may be of no importance as to longevity. Fussell (*Trans. Penna. State Medical Soc. Med. Rec.*, Jan. 1, 1921).

The rules of renal function in disease are not hard and fast. The classification of cases of chronic nephritis is imperfect. There are many atypical cases probably due to previous infections. The outlook in these cases is modified by the extent of fibrosis; when this is limited, life may not be shortened. Many of the arterial hypertension cases have endured for many years without appreciably deteriorating. Cases of cyanotic kidney due to cardiac disease, showing albumin and casts, clear up quickly when the heart improves. The prognosis in confirmed chronic parenchymatous nephritis is exceedingly grave, though not altogether hopeless. In the interstitial cases, the outlook is at times guardedly favorable if recognized early. J. M. Anders (*Med. Rec.*, Jan. 1, 1921).

PATHOLOGY.—There are several types of kidney included in this disease, yet in all the changes of structure are essentially identical, and the variations, when they occur, depend upon the cause and duration of the nephritis.

The large white kidney (without waxy degeneration) may be either normal in size or enlarged, and is pale or yellowish in color. The surface is smooth and the capsule is easily stripped off. On section the cortex appears broader than normally, and is either yellowish white throughout or may present opaque yellowish or whitish areas with mottlings of red. In some cases the pyramids are congested. The following changes may commonly be observed microscopically: The renal epithelium is swollen, hyaline, granular, or fatty, and is more or less disintegrated or flattened; there is an enlargement of the glomeruli, owing to the growth of the capsule-cells and of the cells covering the capillaries, and, in certain cases, as a result of the connective-tissue thickenings of the capsule, the tuft of capillaries is atrophied. There is some thickening of the arterial walls, and a moderate growth of connective tissue may be noted in patches around the glomeruli and tubules. The latter contain hyaline and granular casts.

In post-mortem examination of several cases in which chronic nephritis was attended by hemorrhages the writer found that the bleeding came from the renal pelves. The writer reports a similar case. A man aged 55 years, presenting a typical clinical picture of chronic interstitial nephritis, had on a number of occasions quite marked hematuria. The first bleeding occurred in conjunction with a transient hemiplegia coming on while straining at stool, and the last with a fatal apoplectic attack. Careful microscopic examination of the renal pelves showed three extensive submucous blood extravasations which could be definitely traced to small ruptured veins. The point is of importance, since hemorrhages are usually ascribed to diapedesis. Israel

has suggested that the bleeding may be due to a sudden arterial hyperemia, basing his view upon observations made during operations. The writer points out that during unusual exertion, such as straining at stool, there is increased arterial tension and at the same time venous congestion, both factors probably being of importance in causing the rupture of the veins. Kusumato (*Arch. f. klin. Med.*, Bd. lxxxix, S. 405, 1907).

The small white kidney (secondary contracted kidney) is, in most instances, probably a later stage of the preceding condition, in which the epithelial degeneration becomes more pronounced, and the connective-tissue growth and the resultant cicatricial contraction become prominent features. The kidneys are about normal in size; owing to a shrinkage in the large white kidney, the surface is slightly granular and the capsule proportionately adherent. In color they are usually grayish or yellowish (pale granular), and there may be a certain amount of red mottling. The consistency is firmer than that of the large white kidney, and the surface, on section, shows, in the somewhat narrowed cortex, yellowish-white foci of fatty-degenerated epithelium; hence the term "small, granular, fatty kidney." Microscopically we find extensive degeneration and disintegration of the epithelium of the glomeruli and convoluted tubules, atrophy of the parenchyma, and a corresponding increase in the interstitial connective tissue. There may be an associated waxy degeneration.

In all cases of atrophic nephritis there is hyperplasia of the suprarenal capsules, which in the initial stages is especially characterized by an adenomatous proliferation of the glomerular layer and by the appearance of a limited and encysted hyperplastic nodule of the fasciculated layer; then by the eruption of badly defined hy-

perplastic nodules appearing simultaneously at many points of the same capsule, and, finally, by the complete hyperplasia or perhaps by an adenoma with hyperplasia of all the rest of the gland, which cannot be confounded with an ordinary fatty adenoma. Aubertin and Ambard, Widal and Boïdin and Vaquez (*Semaine méd.*, No. 31, p. 369, 1905).

The large red or variegated kidney of chronic hemorrhagic nephritis forms a third variety. The kidneys are found, as a rule, enlarged, red, swelled, and congested-looking or mottled; frequently they are "bumpy," or slightly bosselated. The capsule is slightly adherent to the depressions between the bosses. The section shows congested portions and gray or yellow spots corresponding to the anemic and fatty-degenerated portions. Red spots, due to small hemorrhage, may also be noticed on both the outer and cut surfaces of the kidney, and small cortical hemorrhagic areas or striations, brownish red in color, are distinctive. Microscopically the appearances are those of acute nephritis superadded to those of the large white kidney, and consist of fatty granular degeneration, epithelial proliferation, atrophied capillary tufts, thickened glomeruli capsules, and, in some places, a growth of interstitial fibrous tissue. In either place inflammatory edema and cellular infiltration of the intertubular tissue may be noted, as well as the dilated tufts of capillaries with surrounding cellular hyperplasia. This variety of chronic nephritis is frequently seen in inebriates.

The writer found, in a carefully studied series of autopsies, that the degree of heart hypertrophy in chronic nephritis could not be referred to the obliteration of the capillaries of the kidney, as Loeb and others have claimed. In the red granular kidney, which is almost con-

stantly associated with arterial hypertension and heart hypertrophy, the writer found, in fact, less destruction of glomeruli than in the secondarily contracted kidney of parenchymatous nephritis, a form which not uncommonly fails to produce marked circulatory changes. The very extensive destruction of the glomeruli in amyloid kidneys was found to occasion no heart hypertrophy whatsoever. Jores (*Verhandl. d. deut. path. Gesellsch.*, Bd. xii, S. 187, 1908).

The majority of nephritis subjects show a more or less cloudy blood-serum during the period in which their urine contains lipoids. The only exception is nephritis from sublimate poisoning, the serum remaining clear throughout the process. The hypercholesterinemia of nephritis is probably due to the concomitant hepatic changes which prevent the physiological elimination of the lipoids. The authors detected a hypercholesterinemia in all nephritides accompanied by albuminuric retinitis. They believe this condition of the blood to be absolutely necessary for the production of the ocular complication. Kollert and Finger (*Münch. med. Woch.*, July 23, 1918).

PROGNOSIS.—The prognosis is invariably bad, though life may, in certain cases, be prolonged. Death may occur in severe cases in from three months to a year, from uremia, dropsy, dilatation of the heart, or from other complications. Cases of a year's duration seldom recover, and those in which advanced secondary contraction of the kidney may be assumed may be considered hopeless; they often terminate suddenly. Rarely there may be a complete recovery; this occurs particularly in children following an attack of scarlet fever. According to the quantity of urine passed in the twenty-four hours, and the amount and persistence of the albumin, is the prognosis made, as well

as upon the degree of cardiovascular and retinal changes. Relapses may occur in apparently favorable cases, and acute attacks may supervene.

In acute nephritis one should never give up a case until the patient is dead, but chronic glomerular nephritis, when the eyes are affected, almost always leads to death in 12 months. In chronic vascular nephritis life may be prolonged for many years and the patient live a life of considerable usefulness. The writer approves of Post's dictum that when there are edema and urinary changes looking like chronic nephritis, but with a normal heart, syphilis should be suspected and a Wassermann done. R. C. Cabot (*Med. Standard*, Oct., 1917).

TREATMENT.—This is conducted much as in acute nephritis. The uremia and dropsy are treated symptomatically. The diet is of great moment, skimmed milk and buttermilk being depended on as much as possible when the dropsy is marked. When the dropsy is slight, more solid food, meat in extreme moderation, eggs, vegetables, and fruits, and an outdoor life should be recommended. The reduction or complete absence of salt in the diet has a strong influence in diminishing edema. Prolonged, sudden exercise and severe exercise should be prohibited.

A diet adequate in calories, protein, mineral elements, and food accessories results in a happier attitude on the part of the patient, while supplying all the requisite vitamins and the complementing of biologically incomplete proteins. The total daily ash constituents should be decidedly alkaline and rich in calcium. Foods high in phosphorus were partly barred, as were also foods of striking flavors. The day's energy requirement should add up at least 2000 calories, and the protein should not

exceed 60 Gm. (2 ounces). Chase and Rose (*Trans. Amer. Med. Assoc.*; *N. Y. Med. Jour.*, June 23, 1917).

Where the patient eliminates nitrogen well, meat need not be omitted from the diet; similarly, if elimination of salt is not impaired, a salt-free diet need not be insisted upon. J. H. Barach (*Arch. of Diag.*, July, 1916).

Acute glomerulitis requires an intake of fluids of about 3 pints (1½ liters) daily, as failure to supply this amount favors azotemia. Should the latter develop the intake should be increased; but too much water has been known to precipitate convulsive uremia. When the condition has become chronic water intake and choice of foods cut little figure; it is sufficient to avoid dietetic excesses. The polyuria naturally present should be encouraged by an intake of 2½ to 3 liters (quarts) of water daily, unless contraindicated by the state of the circulatory organs. Nitrogen must be cut down to from 3 to 5 grams (¾ to 1¼ drams) daily, but never in the form of milk (1 quart alone contains 5.5 grams of nitrogen). Umber (*Berl. klin. Woch.*, Nov. 20, 1916).

More freedom in the allowance of protein than is recommended in the text-book nephritis diet may be of apparently great advantage in the individual case. Thyroid extract has, perhaps, a great value in the treatment of nephritis. If given carefully, its administration is safe. It should receive more attention than has heretofore been accorded it. Phipps (*Boston Med. and Surg. Jour.*; *Amer. Med.*, Dec., 1916).

Edema in chronic parenchymatous nephritis is ascribed by the author to the loss of protein from the blood serum through the continuous albuminuria causing a decrease in the osmotic pressure of the blood. The treatment should be to increase the protein content of the blood and to remove or cause the reabsorption by the tissues of the excessive lipoids. The former is accomplished by a

massive infusion or transfusion of healthy blood accompanied by removal of an equal quantity of blood from the patient, or by a high protein and fat poor diet. The latter consists of lean veal, lean ham, whites of eggs, oysters, gelatin, lima beans, lentils, split peas, green peas, mushrooms, rice, oatmeal, bananas, skimmed milk, coffee, tea, and cocoa, with restricted fluids and only enough salt to make the food palatable. The daily amount of calories runs from 1280 to 2500 and the daily amount of proteins from 120 to 240 grams (4 to 8 ounces); of unavoidable fats, from 20 to 40 grams (10 drams); of carbohydrates, from 150 to 300 grams (5 to 10 ounces). Other articles of food are added gradually as conditions allow. A. A. Epstein (Amer. Jour. Med. Sci., Nov., 1917).

Various examinations, correlated with metabolism studies of the same patients, showed the following: Edema plus retinal edema or low phthalein index indicates chloride retention. Elevated blood-pressure plus retinitis or low phthalein index indicates nitrogen retention. Elevated blood-pressure plus edema indicates chloride and, probably, nitrogen retention. Elevated blood-pressure plus edema plus low phthalein index indicates chlorides and nitrogen retention.

Having found out what type of physiologic renal defect a given case represents the principle of treatment is to protect the weakened function. In chloride retention the rational procedure is to limit the amount of sodium chloride ingested to within the amount the kidneys can excrete. The diet may contain fruit, milk, cereals, sweet butter, and unsalted bread: Breakfast: Apple, baked or stewed; a cooked cereal (no salt added) with cream and sugar; unsalted bread toasted, sweet butter; caffeine-free coffee with cream. Dinner: Cream vegetable soup; two eggs as omelette with tomato or onion; unsalted bread and butter; rice or tapioca pudding. Supper:

Cereal with milk; unsalted bread and butter; stewed fruit. With this method many patients show prompt improvement by diuresis and a rapid subsidence of edema.

Next, all cases of this type must be most carefully examined for foci of infection; occasionally such excellent results are secured that the chance can not be neglected.

The salt lost by nephritics from the hot pack or sweat bath is very slight in amount. Free diaphoresis will in some cases induce uremic symptoms. A hot compress over the kidney region will produce the same result as a hot pack and is devoid of danger and of weakening effect.

In chronic nephritis with nitrogen retention and high blood-pressure only a complete revision and rearrangement of the life and habits of the patient is beneficial. Both marked reduction of diet and a curtailment of business activity are indispensable. A surplus of rest in bed, i.e., much more than the conventional 8 hours, is also necessary. A low protein diet the author has used in such cases consists of a daily allowance of 1 pint ($\frac{1}{2}$ liter) of milk, 4 slices of bread, 2 potatoes, rice, green vegetables, butter, fruit, and sugar. Taken in ordinary quantities this approximates 45 grams ($1\frac{1}{2}$ ounces) of protein daily (7 to 8 grams— $1\frac{1}{2}$ to 2 drams—of nitrogen). In very sick patients it should be reduced.

The second principle in treatment is allied so-called "failure of concentration." It is best when commencing the treatment to give 2 quarts (liters) of fluid a day for 2 days, and collect and measure the urine each day in order to find out whether water is well excreted. If water is excreted freely then the fluid should be gradually increased up to 3 or even 4 liters per day. Where edema results from this "forced fluid" method, correction of this symptom can usually be effected by the use of digitalis. If, however, water is not well excreted, one should try the effect of

"drink days"—2 or 3 days a week when the intake is considerably augmented. A moderate amount of edema is not a sufficient reason for reduction in water ingestion. By contrast with the sequelæ of marked nitrogen retention, edema is relatively insignificant. N. B. Foster (Jour. Mich. State Med. Soc., May, 1917).

The 2 principal guides to treatment in chronic Bright's disease are the general condition of the patient as it is influenced by the progress of the affection and the rate of metabolic excretion as determined by modern methods of examination. The amount of urea excreted in the 24 hours should be carefully and repeatedly estimated. Substances which, like urea, creatinine pigments, hippuric acid, and phosphates, are excreted with difficulty should be allowed in minimal amounts. To avoid the ill effects of phosphoric acid, Von Noorden recommends that **calcium carbonate** be added to substances containing it.

A mixed diet is of advantage with proteins in quite limited amounts. Mercury in all its forms should be omitted. Sajous claims that favorable results have been reported in about one-half the cases of chronic nephritis in which **kidney preparations** were used.

One may use a maceration or, more conveniently, a tablet known as **nephritin**, 10 to 15 5-grain (0.3 Gm.) tablets daily, preferably between meals. **Salvarsan** has yielded encouraging results in cases of syphilitic origin. **Capsule-splitting** has been frequently followed by cessation of hemorrhage in chronic Bright's disease. Primary foci of infection in the teeth and tonsils should receive attention. In cases without marked edema considerable water should be allowed. When dropsy exists, the intake should not exceed a liter (quart) per diem, and a salt-free or salt-poor diet be given. **Digitalis** and the salts of **potassium**, especially the **citrate**, are safest as diu-

retics. The **Karrell diet**, which consists in giving the patients 200 c.c. of raw or boiled milk 4 times daily, at 8 A.M., 12, 4, and 8 P.M., and nothing else, is warmly advocated by some. It should be kept up for a week, then gradually relaxed. J. M. Anders (Therap. Gaz., Oct., 1917).

The writer's practical experience has been that a moderate amount of salt in the diet is not harmful. In the use of water the tendency was to the extreme; by increase of the watery content of the blood a secondary danger to the kidney function is produced by the consequent rise in blood pressure. Effervescent beverages hold a certain element of danger in their stimulative character. The state of the digestion is of exceeding importance in Bright's disease. W. E. Hughes (Trans. Phila. Co. Med. Soc.; Med. Rec., July 20, 1918).

Necessity of study, by every method of research, to determine the cause of nephritis emphasized. In treatment much can be accomplished by a proper dietary, and the writer advocates 1 day of starvation a week. The usual quantities of fluid should be given, but the tax of elimination reduced with the lessened food intake. Regarding drugs, he strongly advises the use of **pilocarpine**, which results in greater elimination of solids and in increase of the specific gravity. The essential point in nephritis is to seek the cause of the abnormal content in the blood. W. D. Robinson (Trans. Phila. Co. Med. Soc.; N. Y. Med. Jour., Dec. 7, 1918).

Woolens should be worn next to the skin, and residence in a warm, dry climate may aid in extending life.

Nitroglycerin may be needed in cases with contracted and tense arteries, and with a tendency to uremic twitchings; **digitalis** may be useful in cardiac weakness. **Basham's mixture** for the anemia and unirritating diuretics will prove of value, and

strontium lactate, in doses of from 15 to 20 grains (0.97 to 1.3 Gm.) three or four times daily, may be tried in some cases.

The writer commends the following for the management and treatment of chronic Bright's disease. In slight cases no medicine may be required, but if anemia is present an occasional chalybeate course is advisable. One of the following prescriptions may be ordered:—

℞ *Solution of ferric acetate*, B. P... ℥xv (0.90 c.c.).
Glycerin 3j (4 c.c.).
Solution of ammonium acetate 3ss (15 c.c.).
Infusion of calumba,
 q. s. ad ... 3j (30 c.c.).
 M. Take twice or thrice a day.

℞ *Reduced iron*. gr. xx (1.3 Gm.).
 Pone in caps. no. xx.
 Sig.: One three times a day.

℞ *Ferrous sulphate* gr. iss (0.1 Gm.).
Magnesium sulphate ... 3j (4 Gm.).
Diluted sulphuric acid. ℥x (0.6 c.c.).
Peppermint water,
 q. s. ad 3j (30 c.c.).
 M. Take three times a day.

The bowels must be kept moderately open. The kind and amount of aperient must be determined on general considerations. In all cases in which the arterial tension is high the author gives a mild mercurial purge at intervals of a week or ten days. The writer recommends:—

℞ *Mass of mercury* gr. ij (0.13 Gm.).
Extract of euonymus .. gr. iss (0.1 Gm.).
Resin of podophyllum gr. ½ (0.0108 Gm.).
Compound rhubarb pill. gr. ij (0.13 Gm.).
 M. et ft. pil. no. j.

A frequent symptom in all forms except the pure cirrhotic kidney is the presence of anasarca. If it is slight, it calls for no special treat-

ment; if it tends to increase, it is desirable to withdraw sodium chloride from the diet as much as possible. No salt is to be added to the food at table, and the bread and other articles of food are to be prepared without it. The following mixture may be prescribed:—

℞ *Theocine sodium acetate* gr. v (0.32 Gm.).
Caffeine gr. ij (0.13 Gm.).
Ammonium benzoate ... gr. v (0.32 Gm.).
Chloroform water,
 q. s. ad 3j (30 c.c.).

M. Take this every four or six hours.

Or, if the heart is dilated:—

℞ *Infusion of digitalis* 3j (4 c.c.).
Potassium citrate gr. xv (0.97 Gm.).
Spirit of chloroform . ℥x (0.6 c.c.).
Infusion of buchu,
 q. s. ad 3j (30 c.c.).

M. Take every six hours.

In cases with much dropsy the most useful medicine is the well-known Baillies pill:—

℞ *Mass of mercury, Pulverized digitalis, Pulverized squills, of each* gr. j (0.065 Gm.).

M. et ft. pil.

Sig.: Take every six hours.

Bradshaw (Liverpool Medico-Chir. Jour., Jan., 1910).

Hot Nauheim baths cause a relaxation of the entire muscular tissue, as evidenced by the fact that after taking from 4 to 5 baths patients are unable to do more than a small percentage of the walking or other exertion of which they were capable before beginning the baths. The baths also relax the peripheral circulation, and this effect may, and possibly does, extend to all tissues of the body. Nauheim baths also cause marked elimination, especially through the skin and kidneys. The writer has seen patients, who came to Nauheim with a skin almost as

dry as a sheet of parchment, after two, three, or four weeks of bathing have an active skin. The attendant increased elimination through the skin doubtless helps lessen albuminuria and lower blood-pressure. Newton (Amer. Jour. Med. Sci., April, 1912).

Physiologic rest for the injured or overworked kidney, a **diet poor in protein and in sodium chloride**, are advocated by the writer. Protein calories are replaced by carbohydrate and to a less extent by fats. Fluid intake is set at a level of about 1500 c.c. per 24 hours. The exact degree of reduction in protein, salt and fluid should vary with the degree of the nephritic process. Catharsis to give free, not loose, movements is needed for the average nephritic. Diuretics have little place in the treatment. Hypertension requires no particular therapeutics other than the diet, baths, catharsis, etc., already described. Edema in nephritis is met by reduction in fluid intake and restriction of protein and especially of salt in the diet. The high protein diet advised by Epstein (1917) for edematous nephritics, did not, in the writer's experience, give good results. The alkaline treatment of Fischer was also disappointing. Continued catharsis sometimes helps. When edema is marked, mechanical removal gives prompt, but, as a rule, only temporary relief. With a normal heart and edema from renal insufficiency, the writer has never seen diuresis from digitalis, and rarely from diuretic drugs. H. A. Christian (So. Med. Jour., Aug., 1920).

Methylene blue has also given satisfaction in some cases.

NON-EXUDATIVE CHRONIC NEPHRITIS, or **CHRONIC INTERSTITIAL NEPHRITIS**, also termed **Chronic Bright's Disease**; **Primary or Genuine Contracted Kidney**; **Cirrhotic Kidney**; **Red Granular Kidney**; **Chronic Productive Diffuse Nephritis without Exudation**; **Gouty Kidney**.

DEFINITION.—A chronic diffuse inflammation of the kidneys, indicated by a growth of connective tissue in the stroma, degeneration and atrophy of the renal parenchyma, and by marked changes in the cardiovascular system.

SYMPTOMS.—The symptoms may remain latent for a considerable time, even for years, while the morbid productive changes are gradually effected in the kidneys. They may not become evident until late in life, even though the kidneys may be in an advanced state of degeneration. Some complicating condition may also supervene, as pericarditis or pneumonia, causing the development of grave renal symptoms. As a rule, however, uremia makes its appearance with headache, stupor, or convulsions, dyspnea, nausea and vomiting, and a tense pulse. This seizure may be recovered from. There is now an *interim*, of variable duration, in which there are drowsiness, lassitude, a disordered digestion, headache, failing vision, dyspnea, and frequent micturition, with a more or less impaired general health. Then follows another uremic seizure, still more severe, if not fatal. If not fatal, the general health is still more reduced, and confinement to the house or bed is necessary; at last the vital forces can no longer compensate for the destruction of the renal parenchyma. Contracted kidney may sometimes first be manifested by spasmodic dyspnea (uremic; cardiac). There is a marked gradual onset of periods of drowsiness during the day that are uncontrollable; an attack of hemiplegia may be the first sign of the disease. In other cases a progressive loss of flesh and strength, with a dry, harsh, wrinkled skin, may be, from the beginning, the only clinical features, until death results from

sheer feebleness and emaciation. The variability and involvement of the symptoms render it advisable to describe them under the various systemic divisions.

There is an increase in the daily quantity of urine excreted so great that it causes a frequent desire to micturate not only during the daytime, but two or three times through the night. This may be aggravated by the hyperacidity of the urine and by the irritability of the prostate gland (especially in advanced years) that are so often associated with renal cirrhosis. The total quantity of urine for the twenty-four hours may measure several quarts in marked cases of the disease. It may be slightly decreased early in the attack, when the degeneration and destruction of the parenchyma are in their incipency; but, as the "blood-flow to the parts that remain must, *ceteris paribus*, be as great as it would have been to the whole of the organs if they had been intact," excessive pressure is brought to bear within the capillaries, owing to the compensating cardiac hypertrophy, and the secretion of the urine, especially of the watery elements, becomes more active. Diabetes may be suggested by the polyuria, but the urine is clear and pale yellow in color, the specific gravity being seldom above 1010 or 1012, and it may be as low as 1002 or 1005. Albumin occurs in traces only, or may even be absent altogether (glomerular atrophy); this is noted especially in the urine voided in the early morning.

Acute indigestion as an important symptom in chronic interstitial nephritis. "No albumin" does not mean "no nephritis." Increased twenty-four-hour output of urine with persistent low gravity, associated with gastric disturbances, should strongly

suggest involvement of the kidneys. Malcolm Seymour (Boston Med. and Surg. Jour., June 6, 1912).

The urea is diminished, and there is little or no sediment. On careful examination, microscopically, there may be found a few casts (usually narrow hyaline), perhaps some leucocytes, and, rarely, a few red blood-cells. Late in the disease or in the presence of a uremic exacerbation or a complicating inflammation, the urine may be diminished in quantity, the albumin increased, and numerous casts be found in the more apparent sediment. Hematuria is a rare condition.

The profuse hematuria and colicky pains observed in nephritis are so characteristic of stone in the kidney that they may be very misleading. Besides nephrolithiasis, profuse hematuria occurs in tumor and tuberculosis and some rare conditions. In 562 cases of chronic nephritis studied in the Königsberg Klinik, the writer found blood in the urinary sediment in 190 (35 per cent.), and in 11 of these the hemorrhage was profuse, in some accompanied by colicky pain. The diagnoses in 3 of these cases were confirmed at autopsy and in all the clinical symptoms were characteristic of chronic nephritis. Askanazy (Zeit. f. klin. Med., Bd. lviii, S. 432, 1906).

Epistaxis may occur and constitute a serious symptom.

Sudden edema of the larynx may also supervene, and is always a grave condition. Transudations into the pleural sac (hydrothorax) and the lungs may precede the fatal termination. Dyspnea is either uremic or cardiac and is usually worse at night; a true orthopnea, with Cheyne-Stokes breathing, may be observed in association with uremic stupor and coma, and near the end of the patient's life.

The signs of hypertrophy of the heart

(particularly of the left ventricle) may be elicited, though symptoms referable to the heart itself are absent, unless dilatation and feebleness, sudden arterial contraction, or endocarditis occur. Inspection and palpation show the apex-beat to be displaced downward and to the left, and the impulse to be increased, heaving, and rather circumscribed. In cases of coexisting emphysema, and later, when dilatation may eclipse the hypertrophy, these signs may become less evident. The left border of deep cardiac dullness extends outside the nipple-line in the fifth or sixth interspace.

Personal case in which the diagnosis of heart-block upon an interstitial nephritis was warranted. The convulsions; the inharmonious heart action; the compromise, somewhat, of kidney function,—all in some way related,—seemed also based upon the presence of Bright's disease with arteriosclerosis,—cerebral, cardiac, and nephritic. E. W. Robertson and J. W. Robertson (Va. Med. Semi-monthly, Oct. 13, 1911).

The first sound of the heart is loud and may be reduplicated. Accentuation of the aortic second sound is a distinctive sign, and indicates increased vascular tension; it may have a metallic quality in some cases. There may also develop a mitral systolic murmur as the result of relative insufficiency. There is increased tension of the pulse, the latter being hard, persistent, and incompressible; the pulse-wave is also increased in duration (*pulsus tardus*). The systolic blood-pressure is decidedly elevated, often exceeding 200 mm. Hg. Most of the palpable arteries are hard, thickened, and tortuous, owing to the arteriosclerosis.

Gastric symptoms are among the most common early symptoms of nephritis. In cases with obscure

gastric disturbances, chemical examination of the blood was found very valuable. Several cases are reported in which estimation of the blood creatinin not only showed the patient had severe nephritis but gave a fatal prognosis. In some of the earlier cases the blood uric acid was of value as an early diagnostic sign. A. F. Chace (Amer. Jour. Med. Sci., June, 1917).

Senile nephritis causes many symptoms in other organs, while giving little evidence of renal disease. Minor symptoms which may become severe and classed as complications are "dead fingers," cramps in the calves of the legs, deafness, a sensation of electric shock on lying down, sensitiveness to cold, and nocturnal micturition. Uremia may affect one organ only, as in gastric, renal, or cerebral uremia. Other complications are indigestion, gastrointestinal disorders, pyorrhea alveolaris, neuritis and neuralgia, cerebral symptoms, and uremic fever. Many of these conditions improve when attention is given to the diseased kidneys. The urinary picture may be clear on some days and obscure or entirely hidden on others. M. W. Thewlis (Med. Rev. of Rev., Sept., 1918).

As soon as compensation fails, symptoms of breathlessness on exertion, palpitation, and the like appear; often these occur in paroxysms and constitute "cardiac asthma." The resulting stasis causes a transudation into the lungs (bronchorrhea, pulmonary edema) and later to edema of the extremities.

Since they are indicative, as a rule, of grave uremia, the symptoms referable to the nervous system are of great importance. There may be neuralgic pains throughout the body, especially of the calf muscles, and insomnia, and cephalalgia is frequent. Later great drowsiness is often a premonition of uremic coma. Muscular twitchings may precede convulsions, and should attract

attention to the imminent danger. Cerebral apoplexy with hemiplegia may form the first symptom of contracted kidney, and is apt to occur in cases of marked hardening and weakening of the arteries. Hemorrhagic pachymeningitis and hemorrhage into the brain-substance may also occur. The hemiplegia may last until the end, or it may disappear soon and be followed by subsequent attacks at intervals. Dieulafoy believes numbness, formication, and pallor of the fingers ("dead finger") as possible early signs of chronic Bright's disease.

In accord with Van Slyke, the authors found that the CO₂-combining power normally varied from 53 to 77 c.c. per 100 c.c. of plasma. In nephritis this was generally 40 to 50, and might fall to as low as 25 shortly preceding death. Lowered CO₂-combining power proved a good index for detecting the dyspnea due to nephritis, and also for gauging the efficacy of treatment of the acidosis of nephritis. Quintard and Fine (*Med. Rec.*, May 27, 1916).

Retention of nitrogen outside of convalescence appears to precede and lead up to either frank uremic manifestations or the graver complications of renal disease. In many instances the metabolic disturbances seemed confined to failure in elimination of nitrogen. If the diet nitrogen is reduced and the intake of fluid is increased, the retained nitrogen is swept out and equilibrium is resumed. Foster and Davis (*Amer. Jour. of Med. Sci.*, Jan., 1916).

The prognosis and duration of renal disease may be foretold from the urea content of the blood. The azotemia passes through successive states, each of which has its special prognosis. The premonitory stage is when the ureosecretory constant is persistingly high but the urea content of the blood is within normal range. In the second stage the urea content of the blood ranges between 0.50 and 1 Gm. This initial azotemia

may retrogress, but often it persists a very long time or passes rapidly into the next stage. As long as it has not passed beyond 1 Gm., the organism seems to adapt itself to it and it is impossible to foretell the duration of the disease. Life can be maintained without apparent disturbance even when only a minimal portion of the parenchyma is left. But when repeated examination shows that the azotemia is permanently above 1 Gm., the condition is extremely grave, and when 2 Gm. is reached and passed, a fatal termination impends. Widal, Weill and Valéry-Radot (*Presse Méd.*, May 23, 1918).

Of the symptoms referable to the special senses nephritic retinitis often forms the earliest evidence of chronic Bright's disease. There may or may not have been present a slight dimness of vision prior to the ophthalmoscopic examination. There is a partial loss of vision in both eyes (amblyopia), and in grave cases sudden and complete blindness may come on (uremic amaurosis) as the result of a neuroretinitis. The optic papilla is swelled, and surrounded by retinal hemorrhages or by white dots and streaks ("feather-splashes").

High pressure and exophthalmos are but evidences of poisoning by perhaps separate toxins. It is well known that uremia may develop in a patient whose blood-pressure is not increased, and it seems very probable that in chronic renal insufficiency several toxins are present in the blood, manifesting themselves in various ways. Among the total admissions of 33 cases of chronic nephritis during the first four months of 1909 at Johns Hopkins University 16 (48.4 per cent.) showed exophthalmos. The exophthalmos varied greatly in degree, as did the gravity of the nephritic process in the various individuals; those cases presenting evidences of serious intoxication (sub-uremic or uremic symptoms) most

frequently showed exophthalmos and one or more of the allied ocular signs,—anisocoria, von Graefe's, Moebius's, or Stellwag's sign. Exophthalmos has been an obvious sign in all of the patients with chronic nephritis which have died in the Johns Hopkins Hospital since January 1, 1909,—7 in number. The authors also observed that the patients with chronic nephritis showing albuminuric retinitis during this period showed invariably exophthalmos, with one or more of the other ocular signs. They emphasize that exophthalmos is but one of several ocular signs which are frequently present in chronic nephritis. Llewellys F. Barker and Frederick M. Hanes (*Amer. Jour. Med. Sci.*, Oct., 1909).

Pigmentation of the retina in nephritis may occur from degenerative changes of the external and middle layers of that membrane, the choriocapillaris being intact. Such degenerative changes of the retina can be regarded as consequences of the nephritis. They are not analogous to the pigmentation which occurs in the fatty cells in fatty infiltration of the retina. The ophthalmoscopic appearances of choroiditis disseminata are sometimes found in changes of the pigment epithelium and retina alone when the choroid itself is healthy. Rachlis (*Klin. Monatsbl. f. Augenheilk.*, Sept., 1910).

There is, as a rule, no edema in renal sclerosis, and when it does occur (as in the ankles and limbs) it is due to cardiac dilatation and failure. The skin is dry, and the pores sometimes appear lustrous with minute scales of urea. The skin has often, also, a cyanotic tinge, with a certain degree of pallor. Troublesome eczema and pruritus are often present, and muscular cramps may make the patient still more uncomfortable; the latter occur at night and especially in the calves of the legs. Other cutaneous disorders may also occur.

Debility and emaciation become extreme with the gradual failure of the general nutrition.

Uremia may supervene at any time, and may even form the first symptom; it may also be sudden and severe in its attack (acute uremia), or gradual, mild, and insidious (chronic). These uremic attacks may be accompanied by either a normal temperature, or by moderate fever; the temperature may even be subnormal, in chronic uremia with prostration, coma, a feeble pulse, and delirium. Uremic diarrhea may also occur.

Among the complications that may occur in the red, granular, and contracted kidney are the following: Pleuritis, endocarditis, pericarditis, cerebral hemorrhage, endarteritis; pneumonia, either lobar or lobular; laryngitis, bronchitis, hepatic cirrhosis, gastritis, enteritis, peritonitis, meningitis, emphysema, phthisis, and mental disorders.

Cases showing that pleurisy, pericarditis, peritonitis, and even meningitis may develop as a complication of chronic nephritis. Likewise in the stage before actual uremia symmetrical fibrillary twitching may be observed or a syndrome suggesting multiple sclerosis and hysteria. In 1 case acute peritonitis developed in the course of a mild chronic nephritis in a middle-aged man. In another case acute meningitis developed in a woman with signs of nephritis. The writer has encountered 3 cases of the complicating pericarditis. In all the above cases the serous membrane became suddenly affected in the midst of apparent health except for the mild nephritis. All the patients died except one man, who passed through two attacks of the pericarditis and succumbed a few months later to a heart lesion. A. Pollak (*Wiener klin. Rundschau*, Bd. xxiv, 1910).

ETIOLOGY.—Sometimes the cause of the slow, primary, diffuse degenera-

tion, atrophy, and fibroid contraction of the kidneys is quite obscure, and in certain cases it would seem to be "only an anticipation of the gradual changes which take place in the organ in extreme old age" (Osler),—the "senile kidney." Heredity undoubtedly plays a part in the causation of certain cases, and its influence has extended down through the third and fourth generations.

Age and sex also exert an influence, the disease being more common in males than in females, and usually beginning near middle life. It is rarely manifested symptomatically until the fiftieth or sixtieth year. A special tendency to sclerotic degeneration of the arteries, from whatever injurious influence, whether chemico-toxic or parasitic, renders the patient more prone to interstitial nephritis, though prolonged irritation by such agents may also cause the disease in persons whose cellular nutrition is usually not defective. Alcoholism, uric acid, and lead, giving rise to chronic poisoning, have all been assigned as causes of the disease.

Chronic malaria and syphilis also probably exert a causative influence.

Habitual overeating and overdrinking no doubt frequently cause granular atrophy and sclerosis of the organ, owing to the imperfect assimilation of the substances ingested and the constant excretion of irritating products by the kidney caused thereby. A widespread cause of the disease is the continuous and even moderate use of alcohol for many years; especially is this true in the case of spirituous liquors. It is probable that the excessive use of red meats in the diet leads to the production of the uric acid that induces the renal condition (uricemia-lithemia) by deranging the hepatic function (Murchison).

Gout may also cause chronic Bright's disease, and is allied to the above; this occurs perhaps more frequently in England than in this country, where lithemia and nervous dyspepsia are more often seen.

Strümpell states that severe articular rheumatism is sometimes followed by contracted kidney.

Anxieties, worries, and the high nervous tension required by modern business activity and by social life (the latter, particularly, in elderly ladies) favor the development of chronic Bright's disease. Associated with these causes are usually to be found an over-indulgence in rich foods and sedentary habits.

The cold, moist climate of New England and the Middle States seems, to Purdy, to predispose to contracted kidney. Hydronephrosis, chronic pyelitis, and chronic congestion of the kidney (of cardiac origin, etc.) may cause a chronic productive nephritis without exudation, though never the true "contracted and red-granular" kidney.

An analysis of the accepted causes of chronic nephritis in man shows that a common factor in many of these is a more or less severe and prolonged stagnation in the renal blood-supply, and, although this factor is often associated with the presence of irritants capable of injuring the tissues of the kidney, an insufficient supply of blood alone will cause first an error in the function and later an alteration in the structure of the kidney. Cardiac disease, bacterial toxins, and metabolic waste-products are probably the causes of the errors in circulation that bring about the changes mentioned. Accordingly, the prophylaxis consists in increasing present efforts to check the spread of infectious disease, and the correction of habits of overstimulation and overwork, so prevalent in large cen-

ters of population. H. Emerson (Archives of Intern. Med., June, 1908).

PATHOLOGY.—The reduction in size and weight is about equal in both organs in genuine primary contraction of the kidneys. The two kidneys may together weigh not over two ounces, and they may be only one-half or one-third the normal size. They are frequently imbedded in thick adipose tissue, and the capsule is thick, opaque, and very adherent; so that, on stripping it off, portions of the renal cortex come away at the same time. The outer surface of the organ is red, irregularly granular, or finely nodular, and occasionally small cysts are present. The tissue is firm, dense, and resistant to the knife. The cut surface shows a thin, atrophied cortex, with dark-reddish streaks alternating with pale portions. The pyramids are darker than the cortex, and are also diminished. In the gouty contracted kidney they show fine striations of sodium urate or of uric acid, or crystals representing uric acid infarctions. The principal changes are seen microscopically to be an increased production of connective tissue, especially in the cortical substance, and a more or less proportionate degeneration and atrophy of the renal parenchyma. The destruction of the latter is due to the circulation of noxious agents, but it is replaced by cicatricial fibrous tissue (Weigert). This new tissue is not uniformly distributed in the cortex, but appears in irregular masses around the shrunken glomeruli or between the tubules. In the pyramids the distribution is more general. The glomeruli are, in many instances, very small and fibrous in advanced cases; in the earlier cases the cells of the tufts and capsules are swelled and multiplied and a small-

celled infiltration may be seen around the glomeruli and tubules. This cellular infiltration later becomes fibrillated and ends in thickening.

The changes that take place in, and the growth of the capillary and intracapillary cells and of those around the tufts are partly responsible for the glomerular atrophy, as are also the capsular thickening and hyaline or waxy degeneration and the thickening and occlusion of arterioles. The tubules show decided changes, some being included in masses of connective tissue, with resulting compression-atrophy and even obliteration of the lumen. Others show constriction by the intertubular connective tissue, the lumen elsewhere thus being increased; this is especially prominent in the granules on the outer surface of the kidney, and little cysts may be seen here and there by the naked eye, as the result of damming back the urine in the tubules thus affected. The epithelium lining these tubules shows granular, fatty, or waxy degeneration, and may be either flattened, cuboid, or swollen in variety. The tubes may contain fatty or granular *débris* and tube-casts.

The growth of fibrous tissue in the walls of the arteries, causing sclerosis, forms an important change in most instances. The intima (endarteritis), media, and adventitia are all thickened by the hyperplasia of connective-tissue elements, and the arteries and capillaries are, in this way, mostly occluded by the obliterating endarteritis or by their conversion into connective tissue. Waxy or hyaline degeneration is also seen. These changes may sometimes form the primary condition that leads to granular and contracted kidneys, and may represent the renal effects of a general arteriosclerosis.

Seven cases of chronic hemorrhagic focal nephritis with sepsis caused by multiple emboli of the glomerulous capillaries by chemotactic, feebly acting bacteria of the chronic ulcerative endocarditis, which was present in all of the cases. In 3 of the 7 cases *Streptococcus viridans* was demonstrated in the blood during life; in the remaining 4 the streptococci were not accurately identified. Pure cases of this kind are in all stages true diffuse glomerulous nephritis and are to be distinguished from diffuse nephritis both clinically and pathologically. Macroscopically they present the picture of the so-called large-spotted kidney. Löhlein (Med. Klinik, March 6, 1910).

Three weeks' experimental retention of urine by ligation of the ureter in rabbits was invariably followed by development of chronic nephritis. After removal of the sound kidney the animals survived for from twelve to eighteen months with persisting albuminuria. Autopsy then invariably revealed extensive sclerosis and aneurism in the aorta, evidently the result of the inevitable increase in the blood-pressure induced by the kidney changes. Even before the blood-pressure rose, substances were discovered in the blood capable of dilating the pupil. Rautenberg (Deut. med. Woch., March 25, 1910).

About half of the chronic nephritides evolving from nephritic processes that have originated during or after an acute infectious disease are predominately parenchymatous; in about 20 per cent. of the cases indurative processes follow in the wake of acute parenchymatous inflammation, or supervene in the presence of subchronic or chronic parenchymatous states, and in about 30 per cent. of the cases amyloid lesions concur with the original parenchymatous affection. The direct transformation of an acute nephritis into a chronic form has been observed in comparatively few instances only; however, the successive transition from an acute nephritic process through sub-

acute and subchronic stages to the chronic condition can be traced clinically with more or less accuracy in a considerable number of cases. Stern (Amer. Jour. Med. Sci., Aug., 1910).

The writer presents a pathological study of 1000 consecutive cases. The so-called primary or genuine contracted kidney represents a disease which is the result of arteriosclerosis in the terminal arterioles of this organ and is closely associated with general arteriosclerosis. There is some reason to believe that the condition as a whole is a toxic one. So far, however, lead is the only substance which seems to bear any definite etiological relation to the general process. Of true primary subacute and chronic inflammations of the kidneys there remain subacute and chronic glomerulonephritis, definitely, in the majority of instances, due to chronic sepsis. Closely related to this, etiologically and anatomically, is the subacute and chronic amyloid kidney (the large, white kidney of other authors). From a combination of the last two conditions there arises the so-called secondary contracted kidney, which, in the author's series, was responsible for 11 out of 37 cases of seriously contracted kidneys. The etiology of the cases of secondary contracted kidney is not quite so clear as that of the more acute conditions, but it is highly probable that chronic sepsis, in the broadest sense, is an important factor. The lesions in subacute and glomerulonephritis and secondary contracted kidneys are practically always hemorrhagic, and in subacute and chronic amyloid kidneys frequently so. The interstitial lesions which are present in these latter conditions begin to develop early, practically simultaneously with the epithelial lesions; it is not likely, therefore, that they should be secondary to them. Ophuls (Archives of Intern. Med., Feb., 1912).

Stress laid on the quantity and biologic value of the albumin circulating in the blood as factors in the production of edema. Retention of

chlorides alone is not enough to account for edema. The blood serum must be in a condition permitting dialysis, and this occurs when its albumin content is below normal from any cause, permitting the transudation through the capillary wall. As edema subsides, the albumin content is found higher, and *vice versa*. The albumin is the regulator and index of the osmotic balance, and the integrity of the liver is indispensable to keep the albumin content normal. The lung being the largest dialyzing membrane in the body, any abrupt change in the osmotic balance is liable to entail intense dialysis here, resulting in acute edema of the lungs. The author cites cases showing the fatal import of abnormally low albumin content in the blood serum. One woman with fatal chronic nephritis had an albumin content always below 0.1 per cent. Facio (*Semana Medica*, Apr. 19, 1917).

In severe nephritis there is high fat in plasma and corpuscles and high lecithin in the corpuscles. These abnormalities are the same as are found in alimentary lipemia and for this reason are probably the result of a retarded assimilation of fat in the blood, which in turn, is thought to be due to a general metabolic disturbance brought about by a lowered "alkali reserve" of the blood and tissues. W. R. Bloor (*Jour. Biol. Chemistry*, Sept., 1917).

Cardiac hypertrophy is an almost constant attendant upon chronic, non-exudative, productive nephritis, and its degree depends upon the extent of the renal, and also of the general arterial, degeneration and sclerosis. *Cor bovinum* has been applied to the organ, on account of its extreme size in this affection. The left ventricle only is hypertrophied in moderate enlargements.

According to Bouveret, 93 per cent. of all cases of interstitial nephritis are accompanied by enlargement of the heart. There are some exceptions, however.

Some conditions prevent the occurrence of the cardiac enlargement, viz., advanced age, tuberculosis, and cachectic states. Again, there occur cases with greatly contracted kidneys, uremic attacks, and death, without cardiac enlargement. These cases are nearly always chlorotic and anemic, with vascular aplasia or a badly developed condition of the heart and vessels. Lancereaux was the first to point out that in badly developed states of the vascular system renal sclerosis does not cause enlargement of the heart.

According to Mayet the only rational theory explaining the frequent coexistence of nephritis and hypertrophy of the heart is that of reflex action: between the glomerular arterioles and the innervation of the heart and vessels there exists an intimate reflex relationship whereby the least constriction of the arterioles reacts upon the vasomotor nerves.

Discussing the pathogenesis of the cardiovascular syndrome in renal disease the author points out that the urinary secretion is the product of an automatic function with a general vasoconstrictor action, and a local vasodilator action for regulating the excretion of the metabolic wastes. In the case of the lungs, the lesser circulation must always give passage to the same quantity of blood, so that in case of obstruction the blood-pressure must be increased and the right heart must enlarge in proportion to the work to be done. The left heart in turn becomes enlarged. The same state of affairs is seen in the kidneys. Just so much blood must be depurated in a certain interval, and if obstruction to the local circulation is present the volume of the heart is increased and a polyuria develops. In the course of a chronic nephritis there occurs an alternation of periods of insufficiency and periods of complete function; this is maintained until there is reached a stage of permanent insufficiency. Silvestri (*Riforma Medica*, Jan. 6, 1917).

In parenchymatous nephritis one may have dyspnea as a result of generalized edema, with hydrothorax or acute pulmonary edema, or when

there is hydremia and chloridemia; in interstitial nephritis, one meets with interference with respiration consequent upon cardiac hypertrophy, dyspnea from asystole due to this hypertrophy, attacks of aortic or coronary asthma, or with or without acute pulmonary edema, and dyspnea in the Cheyne-Stokes form.

Uremia may be superadded to these different conditions, but if their presence does not exclude the possible concomitance of uremia, integrity of the lung and a normal working of the heart at the time of the onset of dyspnea does not, on the other hand, *per se* justify the diagnosis of uremic dyspnea. For this question to be raised there must be a reduction in the proportion of urea and a diminished secretion of urine with azotemia. Bernheim (Med. Press, Feb. 27, 1918).

Certain complications, *e.g.*, cerebral hemorrhage, cirrhosis of the liver, pulmonary emphysema, chronic endocarditis, chronic endarteritis, bronchitis, and gastric catarrh, may be present.

PROGNOSIS.—Chronic interstitial nephritis varies in duration, and in uncomplicated cases it may last for five, ten, twenty, or possibly thirty years. The duration may, however, be very much shortened by complications or intercurrent affections, or the condition may not be appreciated, as often occurs, when the post-mortem examination discovers the characteristic kidneys in one who had no symptoms of renal disease during life and whose death was directly due to some intercurrent affection. Life is destroyed sooner or later by this disease, unless the patient first dies from some intercurrent malady. Irreparable damage to the organs results from the gradual destruction of the renal parenchyma and its replacement by scar-tissue. The fact, how-

ever, that the process is slow, and its duration, therefore, long, allows a preservation of life for many years, and often with comparative comfort. The prognosis depends much upon the general condition of the patient, the cardiovascular system, and upon the presence of uremia and inflammatory complications. A not far distant end is indicated by cardiac dilatation and insufficiency. Hemorrhages, diarrhea, persistent vomiting, nephritic retinitis, coma, and delirium render the prognosis exceedingly grave. Convulsive and apoplectic seizures are often fatal.

The writer speaks of the alarm which is usually caused by this disease in young persons, for with them the convoluted tubes, glomeruli, and interstitial tissue are all affected. Dilute urine in these cases is glomerular urine, and this usually means rise of blood-pressure and fibrosis of the kidney. Death in these cases may be from exhaustion with dropsy and convulsions, or there may be convulsions and no edema. The kidneys in the one case are large and pale, in the other contracted and granular. Nephritis is a disease of temperate climates, especially of those in which the variations are sudden and great. A dry, sunny, and warm climate is most suitable for patients with this disease. Diet is of great importance. Meat is not believed by the author to be harmful; alcohol and condiments need not be forsworn altogether. Appetite is the chief thing to be encouraged, but it is always advisable that no more should be eaten than can be assimilated. As to the mode of life, one must not get fatigued, chilled, nor wet. Pleasures may be taken in moderation, and there should be abundance of fresh air and exercise. W. C. Herringham (Edinburgh Med. Jour., July, 1906).

TREATMENT.—A strict hygienic *régime* following an early appreciation of the disease will, to a considerable de-

gree, prevent the advance of the cirrhotic process. Noxious substances that have an etiological influence must be removed as thoroughly as possible and avoided. Uric acid formation must be reduced by dietetic supervision, alcohol must be interdicted, and lead—when the causative factor—must be prevented from further poisoning the system by a change of occupation. The heart and blood-vessels are also preserved by the diminution of these irritants. The hygienic treatment embraces a regulation of all the habits of the body and the mode of living. The malady is incurable; therefore, the patient himself must be treated, and not the malady. A suitable dietary must be formulated for each individual, and Saundby's rule furnishes a good working principle: "Eat very sparingly of butchers' meat; avoid malt liquors, spirits, and strong wines." An absolute milk diet may be necessary for short periods in the presence of gastric irritability, but undue weakness will be the result of a continued restriction to milk alone.

A light, nourishing diet is, therefore, advisable. Lean meat may be allowed once daily in favorable cases; eggs, vegetables, greens, fruits, and light, well-cooked, farinaceous articles may also be partaken of. Tea, coffee, and cocoa may be drunk in moderation. The use of the natural mineral waters aids in the renal circulation and keeps the kidneys flushed. As a rule, a mixed diet will be advantageous. The nitrogenous and carbohydrate elements (sugars and starches) should be used in moderate amounts, but fruits and pure fats are to be strongly recommended.

If aged patients with nephritis are not ill in bed they should have milk, cereals, and the lighter vegetables, while if in bed an absolute milk diet

is indispensable. Free catharsis is essential. Administration of 6 to 20 tablets of extract of kidney of a pig seemed to give good results and check the process of degeneration. Cabinet baths are useful, particularly in the corpulent and those with much headache, but in the aged caution is required, and the cases must be selected. The elixir of iron, quinine, and strychnine usually works well as a tonic after the eliminative treatment. Fixed habits should not be tampered with, but it is well to keep old people out of bed and to have them work. M. W. Thewlis (Med. Review of Rev., Aug., 1917).

In chronic nephritis efforts to spare the kidney are useless. The writer always gives a full diet except for a reduction of the purin group. Red meats are no worse for nephritis than white meats, but if the patient is told he can eat white meat and nothing else he soon gets tired of eating white meat, and a reduction of meat is thus accomplished indirectly. Meat soups should be forbidden. Salt is not altogether excluded. Patients complain bitterly against not having salt added to the cooking, but get along very well without adding any at table. Daily exercise is essential for the support of the muscular power of the nephritic heart. Drugs and high frequency electricity will reduce the systolic blood-pressure, but almost never the diastolic blood-pressure. R. C. Cabot (Med. Standard, Oct., 1917).

The most common type of kidney disease is the well-known cardiorenal type. The next most frequently seen is that of the middle aged or even younger adult who may have pronounced eye symptoms, edema, low or high blood-pressure, very little kidney reserve, urine loaded with albumin and casts, blood containing 2 or 3 times the normal amount of urea, a high blood sugar, increased blood creatinine, and phosphate retention. Death is commonly preceded by convulsions and uremia. The last frequently seen type is that

of the young or middle aged adult who complains chiefly of edema, weakness, and pallor, with no albuminuria; blood urea and sugar are found low; but the cholesterolin content may be greatly increased. The renal functional capacity is fairly normal to the usual clinical tests, and the patient suffers very little from headache or other symptoms common in renal failure. The first step in the treatment of any type of kidney disease is to eliminate focal infections, as in the tonsils, crowned teeth, and diseased prostates.

In the cardiorenal type, the next most important measure is **rest**, both mental and physical. If the patient has good functional kidney capacity he should be put on a low, general, simple diet. He should be allowed to have some meat and eggs.

In the second clinical type, when severe, the best internal measure is to put the patient at **rest** and give him a limited milk fluid diet as first suggested by **Karell**. The author prescribes for the first few days 1 quart (liter) of milk, 1 pint (500 c.c.) of water, and either another pint of **lime water** or some **salt of calcium**, either the **carbonate** or **lactate**, in 0.5 Gm. (7½ grains) doses several times daily. **Tincture of iron or ferrous carbonate** is also given.

In the third type the diet should be more liberal, and contain a large amount of protein. As many as 8 to 10 ounces (240 to 300 Gm.) of meat might be very helpful. **Fluids** should be **restricted**. If there is evidence of salt retention its use should be curtailed, otherwise it may be sparingly permitted. J. R. Williams (Trans. Med. Soc. State of N. Y.; N. Y. Medical Jour., July 20, 1918).

Persons who take considerable exercise may have a larger amount of food than those who are stout or who lead sedentary lives. Gastric disorders require a liquid diet until the digestion is restored, or the elimination of all but the soft and bland foods. All extremes

of activity (bodily, mental, and emotional) are to be avoided.

Physical **exercise** should be moderate and regular, and, if the climate be warm and dry, it should be taken in the open air. The patient should never be subjected to the vicissitudes of worry, anxiety, or to the tension of competition. Indulgences of whatever nature, if they tend to unbalance self-control or disturb the equanimity of the patient, must be strictly prohibited.

Often life may be prolonged by a change of residence to a warm, dry, and mild **climate**, since the variability and humidity of temperate climates, particularly during the winter season, tend to aggravate the disease. A sea-voyage or a sojourn at some southern European resort may be very beneficial.

Medicinal treatment is employed for the following indications: The bowels should be kept free by the assistance of **laxatives** or by **laxative alkaline mineral waters**. Digestants, with bitter tonics, are useful in cases of furred tongue and indigestion. Acids or alkalis, according to their special indications, may also be used simultaneously.

High vascular tension is to be met by the cautious use of **nitroglycerin** in gradually increasing doses, beginning with 1 minim (0.06 c.c.) three or four times daily, until all danger of rupture of the vessels is over. **Tincture of aconite** is useful if the cardiac muscle is of fair integrity.

The other extreme, of a very low tension that induces dropsy and complications, usually uremic (convulsions, dyspnea, and headache), also calls for therapeutic assistance. Headache, vertigo, and the so-called renal asthma (dyspnea) are also often relieved by **nitroglycerin**.

Low tension, with scanty albuminous urine, edema, and signs of dilatation, requires heart tonics and stimulants, in conjunction with purgatives. **Digitalis** is effective, and especially in infusion, combined with **strychnine nitrate** or with **caffeine citrate**. The dropsy calls for **calomel** and the **salines**.

Uremic symptoms are to be managed, as in acute Bright's disease, by means of free **catharsis** and profuse **sweating**, and occasionally by **venesection**. In convulsions, severe headache, or dyspnea, inhalations of **amyl nitrite** or **chloroform**, or the hypodermic injection of **morphine**, $\frac{1}{8}$ grain (0.0108 Gm.), may be tried. When there is a probable malarial or syphilitic origin, contracted kidney may be benefited by the use of **arsenic** and the **iodides**, respectively. Renaut reports successful results in the treatment of chronic nephritis with a maceration of young **pigs' kidneys**. The adult dose is two kidneys per day (each weighing not over 160 Gm.—5 ounces). Spillmann claims a specific effect for the internal secretion of the kidney as obtained from the venous blood of the organ. No medicaments, however, can ever transform the connective-tissue cells into secreting kidney-cells or restore the destroyed renal parenchyma.

Findings in regard to the metabolism in a patient with chronic nephritis during periods in which she drank ordinary water, and others in which distilled water only was taken. During the ten days in which the patient, a woman of 35, drank only **distilled water**—a total of 12 liters—the output of urine was twice the amount voided during the corresponding periods with ordinary or mineral water. The specific gravity of the urine dropped to nearly one-half. The total amount of albumin elim-

inated increased a trifle during the ten days, while the blood became more condensed. The increased diuresis was not accompanied by an increase in the amount of solid constituents in the urine, but rather the reverse. This speaks against von Noorden's conception of the "flushing out" of the system under copious diuresis. Marcus (Berl. klin. Woch.; Med. Bull., Aug., 1907).

The writer has been using **adrenalin** a considerable time, both as a diuretic and for lessening albuminuria. The majority of his patients did extremely well under it even where the ordinary methods had proved useless. I. Harris (Med. Presse and Circ., June 27, 1917).

Referring to the objection that adrenalin might induce arteriosclerosis, the writer states that he has treated persons of 80 with uremia with 60 drops a day of the 1:1000 solution without interruption over long periods, and without the slightest inconvenience. The pulse seemed more elastic and softer while the **adrenalin** was being taken. Paoloantonio's report of its use in 30 cases of scarlatinal glomerular nephritis is cited. In children it may be given in doses of 2 or 3 drops of the solution for each year of the child's age. It can also be given subcutaneously, or by mouth, in doses of from 10 to 20 drops a day for a child between 5 and 10, according to the severity of the symptoms. Ercolani (Gaz. degli Osped. e della Clin.; Jour. Amer. Med. Assoc., June 2, 1917).

Bright's disease is clearly amenable to **climatic treatment**. The air and soil should be warm, sunny, reasonably dry, and free from malaria and disagreeable atmospheric changes. The locality should be conducive to an out-of-door life the year round, as in southern California. The best course is to advise a warm climate first—one having moderate elevation and only a moderate rainfall, with small diurnal variations in temperature, the humidity being, perhaps, secondary in importance to

temperature and wind. Hinsdale (Urol. and Cutan. Rev., Feb., 1917).

The surgical treatment of Bright's disease, while of undoubted relief and value in relieving pain and prolonging life in some cases, should be recommended only after a careful study of each case. **Decapsulation**, an operation introduced by Edebohls, is the most important of these procedures.

Decapsulation is advised for every sufferer who has reasonable expectation of not less than a month of life without operation. The three conditions given are: First, the clear and unequivocal establishment of the diagnosis; second, the absence in a given case of absolute contraindications to any operation; third, the possibility of securing the services of a surgeon practically familiar with the surgery of the kidney. The earlier in the disease the operation is performed, the better the chances for a cure. Advanced age is not a contraindication if the patient is otherwise in reasonably fair condition. Hypertrophy of the heart must be considered, and as long as the enlargement is not due to dilatation, and as long as the hypertrophy is concentric, an anesthetic may be safely used. It is only when dilatation dominates over hypertrophy that the danger of sudden death is ever present, and the most ominous auscultatory sign is insufficiency of the aortic valves as shown by an intermittent aortic regurgitant murmur occurring every third, fourth, or fifth beat, or even less frequently. If this is present and cannot be removed by medication, operation is inadvisable. In recent years the writer observed marked improvement in cardiac conditions in a number of patients after operation. Albuminuric retinitis must be carefully considered in deciding for or against renal decapsulation. Its importance is due to its being a late sign of the disease, and in recent years he was led by his experience to decline operating when it was well

marked. His experience with renal decapsulation was not very encouraging, and the only condition in which it is advised is in a new chronic nephritis starting up after the former one had been entirely cured. He was able to follow up 99 of the 102 patients operated on by him, an average of five years to each and an elaborate summary of the whole are given. Ten deaths were chargeable to the operation, though this is not positively correct, since all the 10 patients were practically within a few weeks, if not days, of death by the disease. These cases are offset by at least 12 others in which the patients were snatched from impending death by the operation. Thirty-nine deaths occurred at periods remote from the operation, and in none of these was it a factor. Only 11 of these 30 patients were not benefited, and in the others operation did no harm; 6 of the survivors are classed as non-improved, but this is not absolutely correct, as 5 of the 6 are better in general health than before the operation. Of 11 classed as improved, the betterment has been continuous since the operation, and 3 appeared to be on the eve of restoration. The 33 cures of chronic Bright's disease from the operation would, it is stated, justify all the work which has been done, even if no benefit had accrued to the remainder of his patients. It is worth noting that 14 of the 102 patients were physicians and 5 others were members of physician's families, thus showing their confidence in the operation. G. M. Edebohls (Jour. Amer. Med. Assoc., Jan. 16, 1909).

Case of chronic glomerulonephritis in a girl aged 15 years who had marked symptoms of nephritis since her fourteenth year, no disease having pre-existed except scarlet fever during her first year and whooping-cough during her fourth year. **Double decapsulation** was performed, the kidneys at that time being large, soft, regular, yellow, and mottled. The capsule was thin and easily stripped. Marked improvement fol-

lowed, and nothing was complained of for more than fifteen months, when renal symptoms returned gradually, death, however, not occurring for more than three years from the time of the operation. She suffered less, and life was prolonged by the operation. E. Garceau (Boston Med. and Surg. Jour., vol. clx, p. 707, 1909).

For the sole purpose of making the little sufferers more comfortable, and to relieve the anasarca and uremia, the writer operated in 5 children. In 4 out of the 5 the patients were restored to an existence at least simulating health. In no case did the operation endanger life; the recovery from so-called shock and the anesthesia was very prompt. With the exception of 1 case all were carefully selected for the procedure of Edebohls after a reasonable trial of well-known internal methods had failed. The well-being of the patients was restored for greater periods than medicinal agents could have done, and without compromising the recuperative powers of the kidney. The improvement did not set in immediately after the operation, but only after the kidney had become accustomed to the new local circulatory conditions. Koplik (Amer. Jour. Dis. of Children, Oct., 1911).

Dr. Edebohls just before his death was able to trace all but 2 of the 102 cases he had operated upon up to the time of his report. From that time to the time of his death he operated upon 6 additional cases. In addition to these, the writer personally operated upon 12 cases. The results of these 18 cases show:—

Improved	5
Died within two weeks of operation .	2
Died later (unimproved)	2
Cured	8
Unknown	1

Compared with Dr. Edebohls's statistics, this makes the operative mortality slightly more. In his 102 cases the immediate mortality was 10.1 per cent. In this series it is 11½ per cent., or for the whole 127 cases a little over 10 per cent.

Renal **decapsulation** is indicated in all varieties of chronic nephritis in the absence of conditions absolutely contraindicating any surgical procedure. Samuel Lloyd (Southern Med. Jour., April, 1912).

Report of 4 cases of **Edebohls's operation** in parenchymatous nephritis in children. Of 23 cases in children in the literature, 2 were permanently cured, another was well for 2 years, then died of an acute nephritis in no way connected with the previous illness; 2 others were well as long as they were under observation; 9 others were improved. The operation may save life and result in permanent cure in acute nephritis. No child ill with acute nephritis should be allowed to die, therefore, without giving it the advantage or the chance afforded by this operation. It may prolong life for considerable periods in chronic nephritis, and may possibly, in rare instances, result in cure. J. L. Morse (Jour. Amer. Med. Assoc., Aug. 18, 1917).

The writer recommends renal **decapsulation** in cases which fail to improve either clinically or functionally under long continued conservative treatment. It is not a dangerous operation. It is strongly indicated in severe attacks of uremia brought on by anuria, and in these cases saves many lives; also in nephritis dolorosa and in hemorrhagic nephritis; here decapsulation of 1 kidney is sufficient; in all other cases bilateral decapsulation is preferred. Karo (Münch. med. Woch., Oct. 15, 1920).

It is of service in cases of the parenchymatous type, where medical measures have not been successful, and in which pain in the lumbar region is a prominent symptom, thus indicating an increased tension in the cortex.

Post mortems have shown that the resulting scar-tissue surrounding the kidney has been thicker and denser than the normal capsule.

It is, therefore, scarcely to be recommended in the chronic interstitial type, where there already exists an excess of connective tissue with a marked tendency to progression, besides a marked decrease in the parenchyma to carry on the kidney function.

JAMES M. ANDERS,
Philadelphia.

BRILL'S DISEASE. See TYPHUS.

BROMINE AND BROMIDES.

—Bromine is found in saline springs and in sea-water, but is generally obtained from the mother-liquors of salt-works. It occurs in the form of a dark reddish-brown, volatile fluid, emitting pungent and acrid fumes, caustic in action and taste. It is sparingly soluble in water (1 to 28), very soluble in chloroform, and likewise in ether and alcohol, both of which, however, it gradually decomposes. It combines freely with bases to form salts, the principal ones of which, the bromides, are extensively used.

PREPARATIONS AND DOSE.—

The official preparations are the following:—

Potassii bromidum (potassium bromide), colorless, cubical, translucent, non-hygroscopic crystals, having no odor, but a bitter, pungent, saline taste. It contains about 67 per cent. of bromine and is prepared by adding bromine to a potassium solution. It is soluble in about 1.5 parts of water and in 12.5 parts of alcohol at 25° C. Dose 10 to 30 grains (0.65 to 2 Gm.).

The following formula provides a solution which may be used hypodermically without any ill effect and which at the same time is strong enough to furnish an ordinary dose of the salt (15 grains—1 Gm.). The formula follows:—

℞ *Potassium bromide* ʒi ss (45 Gm.).
Sodium sulphate .. ʒss (2 Gm.).
Carbolic acid ℥xv (0.9 c.c.).
Distilled water,
 q. s. ad ʒiij (90 Gm.).
 M. et ft. solutio.

Thirty minims (1.8 c.c.) of a solution prepared after the foregoing formula will contain 15 grains (1 Gm.) of potassium bromide, and this amount is directed to be injected into the front part of the thigh. If it is desired to administer 30 grains (1.8 c.c.) at one dose an injection of 30 minims (2 Gm.) is made in each thigh, the needle being made to penetrate rather deeply. The proportion of bromide should be slightly reduced in the winter, as the cold weather may cause precipitation of some of the salts. This, however, can be overcome by heating the container.

In this solution the carbolic acid acts as a local anesthetic and keeps it sterile, but its principal advantage lies in the prevention of the diapedesis which is generally observed to follow injections of potassium bromide. As for the sodium sulphate, its function is to facilitate absorption and favor the elimination of the carbolic acid. The writer has never noticed any sharp pain follow the injection; in rare cases a slight local edema has been produced, which is easily removed by the application of ichthyol ointment. Rebizzi (*Semaine méd.*, Sept. 23, 1908).

In a study of the influence of lipoids on the solubility of haloid salts the writer found that bromides otherwise insoluble in ether, become dissolved under the influence of organic lipoids or lecithin. This influence is even more pronounced with the iodides, but less so with the chlorides. Iodides are also dissolved by benzine but not the bromides. Yoshitomi (*Acta Scholae Med. Univ. Imp.*, Kyoto, Nov. 30, 1918).

Sodii bromidum (sodium bromide), a white granular powder, which abstracts moisture from the air, and has a saline, somewhat bitter, though not

unpleasant, taste. It contains 27.5 per cent. of bromine and is prepared in the same manner as the potassium salt. It is soluble in 1.7 parts of water and 12.5 parts of alcohol. Dose 10 to 30 grains (0.65 to 2 Gm.).

Ammonii bromidum (ammonium bromide), white or transparent prismatic crystals or powder having a disagreeable, pungent, saline taste. It is prepared by neutralizing hydrobromic acid with ammonia, and is soluble in 1.2 parts of water and 12.5 parts of alcohol. Dose 5 to 30 grains (0.33 to 2 Gm.).

Lithii bromidum (lithium bromide), a white, crystalline salt having a sharp, bitter taste, which deliquesces readily. It is prepared by saturating with a solution of lithium carbonate one of hydrobromic acid and is soluble in 0.6 part of water and readily in alcohol. Dose 5 to 20 grains (0.33 to 1.3 Gm.).

Calcii bromidum (calcium bromide), a white, granular, very deliquescent salt having a pungent, saline taste. It contains 80 per cent. of bromine, the highest of all bromides, is prepared by dissolving calcium carbonate in hydrobromic acid, and is soluble in 0.5 part of water and 1 part of alcohol. Dose 10 to 30 grains (0.65 to 2 Gm.).

Strontii bromidum (strontium bromide), colorless, transparent, very deliquescent crystals, having a bitter, saline taste. It contains 65 per cent. of bromine and is prepared by neutralizing hydrobromic acid with strontium carbonate. It is soluble in 1 part of water and is very soluble in alcohol. Dose 5 to 30 grains (0.33 to 2 Gm.). (The official test for barium as an impurity consists in dissolving 1 Gm. each of the bromide and sodium

acetate in 5 c.c. of water, acidifying slightly with dilute acetic acid, and adding 5 drops of standard potassium dichromate solution. No cloudiness should develop within 3 minutes.)

Bromoformum (bromoform), a colorless, transparent, and heavy liquid having a sweetish taste and ethereal odor. It is prepared by adding bromine to equal parts of caustic potash and methylic alcohol, and as used is composed of 99 parts of absolute bromoform and 1 part of absolute alcohol. It is but slightly soluble in water, but readily so in alcohol and ether, and, being readily changed by light and air, it should be kept in dark, well-stoppered bottles. Dose 1 to 5 minims (0.06 to 3 c.c.).

Simple formula for bromoform and chloroform mixture:—

R <i>Bromoform</i>	18 gr. (1.2 Gm.).
<i>Chloroform</i>	8 min. (0.5 c.c.).
<i>Rum</i>	4 fl. oz. (120 c.c.).

Whereas alcoholic solutions of bromoform precipitate in excess of water, this mixture with chloroform does not precipitate, no matter what are the proportions of water present. Gay (Jour. of Med. of Bordeaux; La Sem. méd., No. 11, 1900).

Acidum hydrobromicum dilutum (dilute hydrobromic acid), a colorless, transparent liquid—or gas in solution—having a strong acid taste. It is a 10 per cent. solution of hydrogen bromide, and miscible in any proportion with water and alcohol. Being volatile and decomposed by light, it should be kept in dark, well-stoppered bottles. Dose 20 minims to 2 fluidrams (1.25 to 8 c.c.).

INCOMPATIBLES.—The bromides should not be combined with strong mineral acids or given in acid mixtures, as decomposition of the bromide salt may occur. Neither

should they be combined with strong oxidizing agents such as potassium chlorate and permanganate and hydrogen peroxide. Strychnine salts are precipitated by bromides. Ammonium bromide should not be prescribed with spirit of nitrous ether.

MODES OF ADMINISTRATION.—Being all more or less irritating to the stomach, the bromides are best given in solution, well diluted. They are all readily soluble, both in water and in alcohol, except potassium bromide, which is soluble only in 180 parts of alcohol. They are not given hypodermically, as the injection of concentrated solutions causes local pain and irritation. They all have a bitter, salty taste. Ammonium bromide is the most unpleasant to take of the commonly used bromides, and sodium bromide the least. All the bromides except potassium and ammonium absorb moisture from the air.

PHYSIOLOGICAL ACTION.—The local action of bromine, especially upon the mucous membranes, is that of a very active corrosive irritant. The effects attending its internal use are best studied through the action of the various bromides, that is to say, of the *bromine ion* they contain.

Nervous System.—On the nervous system the bromides, in moderate therapeutic doses, act as mild depressants to the brain. In larger doses they also depress the spinal cord, especially its sensory side, and perhaps also the peripheral sensory nerve-endings. In the brain the effect is particularly marked on the intellectual centers and the psychomotor areas. Mental activity is reduced; external objects and movements are perceived, but fail to excite any in-

terest. The mind is thus in an apathetic state predisposing to sleep, which, if surrounding conditions be favorable, finally results. The sleep is not very deep, however, and is often not refreshing, the patient feeling dull and heavy for some hours after awakening. The effect on the psychomotor centers has been demonstrated in dogs. Upon exposure of the brain, the application to these areas of an electrical stimulus which would ordinarily cause epileptiform convulsions produces only localized muscular contraction after bromides.

It is characteristic of the effect of bromides on the central nervous system that the communications between the various sensory cells and centers are interfered with by bromide, so that in any reflex action, either in the brain or cord, the response to stimulation is strictly limited and localized. This is exactly opposite to the effect of strychnine, which exaggerates the reflex effects of a stimulus by facilitating its passage to distant sensory nerve centers.

In the spinal cord and the centers of the cranial nerves, full doses of bromides decrease reflex excitability. Nausea is no longer felt when the throat is touched, no winking occurs on touching the conjunctiva after very large doses, while the reflexes of the genital organs are notably reduced. With very large doses, too, general sensation is also diminished, the skin becoming more or less anesthetic, owing to depression both of the sensory centers and nerve-endings. The medullary centers are but little affected by bromides. In the frog the effect of bromides on the spinal cord is much more marked than on the brain. Reflex activity may be

entirely lost at a time when voluntary movements are still made.

Experiments on animals in which serious symptoms were produced by the administration of bromides. The animals developed ataxia progressing to fatal paresis. These symptoms, ordinarily regarded as bromide poisoning, are due to chlorine deficiency and it was possible to save the animals by injecting **sodium chloride**. They recuperated entirely in twenty-four hours with no sign of their previous serious condition. The continuous administration of the bromides causes a considerable retention of bromine ions in the blood. Consequently sodium chloride is excreted in order to prevent the concentration of salts in the blood. The deficiency of the chloride leads to serious consequences, which may be relieved by the injection of **normal saline solution**. In the treatment of epileptics this action is obtained by administering bromides and simultaneously reducing the salt in the food. Wyss (Med. Klin., Bd. xlvii, S. 1749, 1908).

Experiments described by the writers showed that the bromide ions exert a stimulating effect on the respiratory center. Hooker and Macht (Jour. Pharm. and Exper. Therap., Feb., 1918).

Circulation.—No perceptible effect is produced when the bromides are taken by the mouth, even in large doses. Hydrobromic acid injected in animals causes a slight but temporary rise of blood-pressure which has been ascribed to a direct action on the vessel walls, followed, with very large doses, by cardiac depression. Potassium bromide, injected intravenously, tends to depress the heart, but this is because of the potassium rather than the bromide ion.

On the *respiration* bromides cause a slight depression with full doses, breathing becoming slower. The *temperature* is lowered by very large

doses, probably owing to lessened movement. As to *metabolism*, the output of phosphorus-containing compounds in the urine is sometimes decreased, probably owing to lessened nervous activity.

Locally the bromides are mildly irritating. Beside causing salivation and thirst, large amounts irritate the stomach, producing nausea, vomiting, and occasionally diarrhea.

Absorption and Elimination.—The bromides are rapidly absorbed, but very slowly excreted. After a single dose, the urine has been found to contain bromide for as long as two months (more often twenty days). The bromine ion, circulating in the blood, appears to be readily accepted by the tissues as a substitute for a portion of the chlorine ion normally present in them as chlorides, and this probably accounts for the slowness of its elimination. Administration of bromides is followed by increased output of chlorides in the urine, indicating that the former partly replace the latter in the tissues. When bromides are taken continuously, they accumulate in the body. The amount excreted daily increases progressively, however, until, after a certain time, generally in two or three weeks, the amount eliminated in the twenty-four hours equals that taken in, a state of equilibrium being established. A large quantity of bromide is then present in the body, especially in the blood, brain, and kidneys. The acid of the gastric juice then consists partly of hydrobromic acid. The effects of such an accumulation of bromides in the body are those of a single dose in an exaggerated form, and, when especially marked, constitute the condition known as "brom-

ism," to be described later. In addition to passing out in the urine, the bromides are eliminated also through the alimentary tract, slightly through the skin, and, in nursing women, slightly with the milk.

As to the *physiological action of metallic ions in bromides*, they differ considerably:—

Sodium is indifferent or neutral as to action. The amount of it present normally in the body is so large that the addition of a small amount is without effect. The action of sodium bromide is thus practically that of the bromide ion.

Potassium is a depressant to the whole central nervous system and, less markedly, to all muscles, including the heart. The nerve-depressant effect of the bromide in potassium bromide is considerably strengthened by it. The circulatory depressant effect of potassium is hardly noticeable, however, when potassium bromide is taken internally, except on prolonged use; marked depression is seen only when it is injected intravenously in animals. Potassium bromide is a little more irritating locally than sodium bromide.

Ammonium compounds, when injected hypodermically or intravenously, act as a pronounced stimulant to the spinal cord, medullary centers, and heart-muscle, but when taken by the mouth much of this stimulating effect is lost. The effect of the bromine in ammonium bromide is but little modified by it except with large doses. On the brain ammonium does not act as a stimulant, if anything it assists the action of the bromine on this structure. Ammonium bromide, like the potassium salt, is more irritating locally than sodium bromide.

Strontium, i.e., its ion, is but very slightly absorbed from the alimentary canal; hence it has no effect when taken internally, and the only way in which it modifies the action of the bromine in strontium bromide is to delay slightly its absorption into the system, since the salt has to be decomposed before the bromine is absorbed. Strontium is said to be, with calcium bromide, the least irritating of all the bromides.

Calcium may be said to have the same effect as strontium; it remains practically unabsorbed, and slows the action of the corresponding bromide.

Lithium depresses the nervous system and circulation almost like potassium when given intravenously, but in addition it has a special tendency to cause gastrointestinal disturbances on prolonged use. It is readily absorbed.

Zinc (zinc bromide formerly official) acts as an astringent and irritant.

The last three of these salts, as well as dilute hydrobromic acid, are seldom used in therapeutics.

Bromides, given in a single dose or in 2 doses given near together, are retained for quite a time in the organism. In subjects with normal kidneys the largest amounts of the bromine are eliminated during the first 3 days, after which the remainder is eliminated in decreasing amounts. On the thirty-fifth day the quantity eliminated represents only 72 per cent. of the bromine absorbed. The elimination during the first 24 hours was only 3.2 per cent. of the total amount ingested. In subjects with nephritis the elimination was 3 times less during the first 10 days than in subjects with a normal urinary function. W. Authenrieth (Münch. med. Woch., July 9, 1918).

BROMIDE POISONING.—Fatal acute poisoning with bromides is al-

most unknown in man. Enormous single doses produce such symptoms as gastrointestinal pain, nausea and vomiting, thirst, headache, circulatory weakness, low temperature, loss of reflexes, anesthesia of the skin, and especially marked drowsiness; lasting for several days, with slow return to normal as the drug is gradually eliminated.

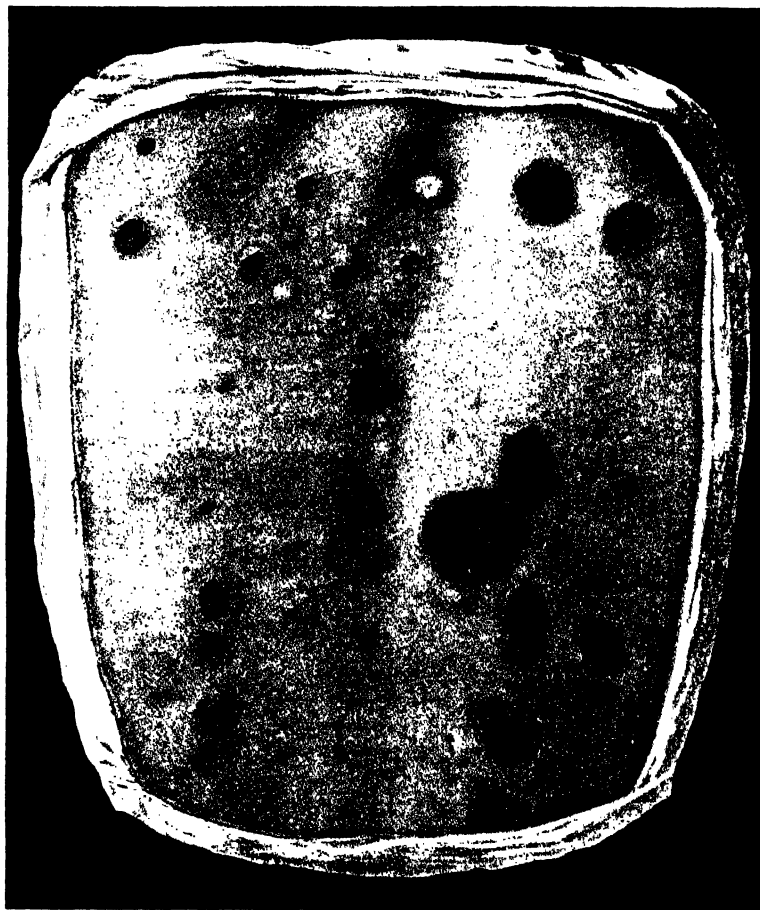
Two cases of bromoform poisoning; the children found lying side by side, with breath smelling strongly of bromoform, with faces pale, eyes closed, pupils contracted, and limbs flaccid. Artificial respiration, brandy, and strychnine hypodermically administered, and lavage with hot water and hot coffee brought consciousness in about one and one-half hours. Stokes (Brit. Med. Jour., May 26, 1900).

Case of bromoform poisoning in a child 16 months old. The points of especial interest were: The rapidity with which unconsciousness came on, and the corresponding rapidity with which the child returned to consciousness, after a period of over four hours; the pinpoint pupils, which might have led to an incorrect diagnosis of opium poisoning. The bromoform administered to the child was not the last in the bottle, and therefore concentrated, as 6 fluidrams (24 c.c.) remained in the ounce bottle, after the second dose. H. K. Dillard, Jr. (Ther. Gaz., April, 1903).

Case of poisoning by bromide of potassium in a woman aged 35 years who was nearly nine months pregnant. She was of a neurotic temperament, but otherwise perfectly healthy. She had suffered from facial neuralgia and was ordered one evening a 6-ounce (180 Gm.) mixture containing 30 grains (2 Gm.) of bromide of potassium in the ounce (30 Gm.): This she placed under her pillow and helped herself to at short intervals during the night. It was afterward found that she had a private store of the drug which she also took, so that

she swallowed altogether about $4\frac{1}{2}$ drams (18 Gm.) of the salt in less than twelve hours. When seen on the following day she was in a very drowsy and semicomatose condition. She could be aroused by speaking loudly to her and answered—apparently without understanding the question—in a hesitating and tremulous manner, but was unable to express herself intelligently on account of aphasia. This was extremely well marked, and but for the history and the absence of other symptoms would have strongly suggested a cerebral lesion. Thus the medicine was referred to as soup, pastry, as cushion, and so on. She seemed conscious that she was using the wrong word and after several repetitions of it would relapse into silence. Left to herself she passed at once into a semicomatose state. The respirations were deep, regular, and slightly stertorous, but not slower than normal. The pupils were normal in size and reacted well to light and to accommodation. The pulse was 76, quite regular, and of good volume and tension. The fetal heart could be heard quite plainly. The knee-jerks were exaggerated and although the muscular movements were slow and feeble the patient was able to leave her bed without assistance and totter about the room. There was no anesthesia of the skin or mucous membranes and she took food readily and with apparent appetite. These conditions continued without any change for two days. On the third day the aphasia had begun to disappear and by the end of the fourth day the patient was practically well. She had no recollection of what had happened during the first two days. No treatment was adopted except the administration of 5-minim (0.3 c.c.) doses of liquor strychninæ every four hours. Three weeks afterward the patient gave birth to a vigorous male infant, the labor being rapid and uneventful.

The case is instructive on account of the well-marked aphasia and the fact that labor and the fetus were



Bromide of Potassium Eruption.

(Atlas de l'Hôpital St. Louis.)

quite unaffected by the drug. The aphasia is difficult to account for. A. C. Stark (*Lancet*, May 2, 1908).

[The physiological action of the bromides as given herein is the prevailing one. The writer's personal views on the subject account for the above phenomena through the cerebral ischemia which relaxation of the deep trunks, those of the splanchnic area, entails. C. E. DE M. S.]

Experiments upon the action of bromides on smooth muscle strips showed they stimulate smooth muscle slightly when the tissue is in a normal, rhythmic condition and markedly when arrhythmic or partly fatigued. Kruse (*Jour. of Pharm. and Exper. Therap.*, Oct., 1919).

BROMISM or CHRONIC BROMINE POISONING results from continuous use of bromides in large doses. The liability to it varies in different persons, the old or emaciated persons being especially susceptible to it. In some cases it appears suddenly after several months of bromide treatment without ill effect. The symptoms are numerous. Prominent among them is a skin eruption, generally of the acne or pustular type, and sometimes quite severe, due to the excretion of the bromide through the skin. In children this may assume the form of small, brownish-red elevations of the skin which are rather characteristic.

Three cases of bromide eruption mistaken for blastomycosis. The lesions in all 3 cases were on the legs and were similar, being pustular and papulopustular. The margins were elevated and crusted, surrounded by bluish-red or pale-red areolæ, in which there were many miliary pustules. In the early stages the bromide eruption is more actively inflammatory, but later the processes in this respect are very much alike, and on a superficial examination the two diseases are clinically counterparts of each other. It is essential in any

case suspected to be one of blastomycosis, in which bromides have been administered, to demonstrate positively the presence of the causative organisms (blastomycetes) before making the diagnosis. O. S. Ormsby (*Jour. Cutan. Dis.*, Oct., 1909).

Bromide eruption may occur in those who are susceptible, independent of the dose of the drug or the length of the administration. The larger the dosage, and the longer the ingestion, the greater is the chance of an outbreak. There are practically no constitutional or subjective symptoms in most cases. Because of the slow elimination, the eruption may continue to appear for some weeks after the drug has been discontinued. Almost any type of eruption may be present; in childhood the lesions are usually larger and more persistent than in adult life. The extremities and the face are the parts most frequently attacked; the most extensive eruption, in the majority of the cases, occurs upon the legs. Lesions have a great tendency to occur at points of previous inflammation, such as on vaccination scars, injuries, etc. F. C. Knowles (*N. Y. Med. Jour.*, March 20, 1909).

There is also an increase of bronchial and nasal secretions, an unpleasant odor of the breath, and similar taste, all believed to be due, at least partly, to liberation of bromine through decomposition of the bromides by body acids. Digestive disturbances due to local irritation by the drug are also complained of, the appetite being lost. There may also be gastric pain. Mental and nervous phenomena also occur; they include pronounced failure of memory, depression of spirits, general indifference, and defective speech, drowsiness, partial insensibility of the skin and mucous membranes, diminished reflexes, and unsteady gait. The facial expression is stupid, and a

marked degree of imbecility is sometimes reached. In advanced cases the respiration is slowed, the temperature lowered, and even the power of voluntary motion and speech is practically lost. Death occasionally results, oftener from infectious disease such as pneumonia, to which the depressed state of the patient predisposes him, than from the direct action of the drug.

TREATMENT OF BROMINE POISONING.—Stopping the drug is soon followed by cessation of the symptoms. The skin eruption due to bromides can often be prevented by giving arsenic along with them, using 1 or 2 minims (0.06 or 0.12 c.c.) of Fowler's solution to each dose of bromides. Strict cleanliness of the skin and occasional purgation are also desirable.

THERAPEUTICS.—The bromides are used mainly for their calmative effects in **general nervousness** and **insomnia**. In moderate degrees of **nervous excitement** and excessive irritability brought on by overwork, grief, or worry, and in **insomnia** due to excitement, bromides are useful as mild depressants, though less certain than chloral hydrate or trional, the bromides not being true hypnotics, but merely favoring sleep by lessening the response to external stimulation. Again, the slowness of their elimination is apt to induce rather prolonged general depression. In **insomnia** due to pain the bromides are of little or no value, except in certain cases of headache, but they enhance the action of morphine, which may be given simultaneously in small doses to alleviate suffering while inducing sleep. Sodium bromide is slightly less irritating to the stomach than the

potassium salt, while acting less powerfully. A mixture of the sodium and ammonium bromides is specially recommended by some:—

℞ *Sodii bromidi*,
Ammonii bromidi ...ãã Ñiv (16 Gm.).
Aquæ fÑj (30 c.c.).
Elixir aromatici...q. s ad fÑiij (90 c.c.).

M. Sig.: Teaspoonful in water before retiring.

The dose of bromide used ranges from 10 grains to 1 dram (0.65 to 4 Gm.); generally 20 to 30 grains (1.3 to 2 Gm.). Peppermint, wintergreen, or preparations containing citric acid are among the best flavoring agents for bromides. Syrups only make the taste more unpleasant.

In **epilepsy** the bromides are used considerably, but often unwisely. In 85 to 90 per cent. of cases the continuous use of bromides will cause diminution in the frequency and violence of the epileptic attacks. In some instances the attacks are entirely removed as long as the drug is used, but return when it is stopped, while in a very small proportion of cases a cure is said to be obtained. They should not be deemed curative, but useful to suppress fits while curative measures are used (Spratling). The bromides act by lowering the excitability of the cortical motor centers which are subject to periods of abnormal irritability—a period now known to represent an effort to rid the blood of spasmogenic toxics.

When pushed in epilepsy, bromide of potassium produces apathy, listlessness, a total lack of interest in surroundings, a dull, sodden facial expression, and if carried still further a mental condition not unlike bromide poisoning. Toxic doses arrest the heart in diastole; the long-continued use of the drug results in a weakened and irritable condition of the heart

and a general impairment of the circulation. Large doses depress respiration. The mucous membrane of the stomach is irritated, and the normal secretion of gastric juice checked. It causes constipation, coated tongue, foul breath, loss of appetite, and not infrequently nausea and diarrhea. Metabolic changes are lessened through depression of the nervous system, and tend to produce anemia. Further, the drug often causes the well-known eruption. Bromide of potassium is to be used when over-excitement of nervous protoplasm is present, but never when the symptoms are due to depression. It is especially to be avoided in so-called psychical equivalent states. The writer has never seen a case of epilepsy cured by a bromide. W. P. Spratling (*Ther. Gaz.*, June, 1903).

The bromides are being increasingly used in **melancholia** and similar conditions. Exact estimation of the degree of brominization is important. When much salt is taken, the bromide has comparatively little action. The relative bromine and chlorine content of the body can be determined by a single blood analysis. In severe **epilepsy**, enough bromides must be given to bring the relative bromine content of the blood up to 20, 25, or even 30 per cent. In the urine the corresponding relative content would be from 15 to 25 per cent. The diet must be salt-poor, reduced to from 5 to 15 Gm. ($1\frac{1}{4}$ to $3\frac{3}{4}$ drams) salt per day. To obtain a 15, 20, 25 or 30 per cent. relative bromine content of the urine, when the patient is getting 5 Gm. ($1\frac{1}{4}$ drams) of sodium chloride a day, the sodium bromide dose should be, respectively, 1.6, 2.2, 3 and 3.8 Gm. (25, 33, 45 and 60 grains). If potassium bromide is used instead of sodium bromide, the dose should be increased by 15 per cent. above these figures. It is the combination of chloride and bromide that is effectual, neither alone, and only their proper combination. Bernoulli (*Corresp. Bl. f. schweizer Aerzte*, Aug. 11, 1917).

[Textbooks on the practice of medicine continue, regardless of the admonitions of men of large experience to the contrary, to advocate the use of bromides as a curative measure. Percy Bryant, many years ago, emphasized the fact that the bromides had added another disease in many epileptics, namely, bromism. Spratling, as the result of a close study of several thousand cases at the Craig Colony, concluded that "we must not only regard the bromides as powerless to cure epilepsy," but also "as capable of doing as much harm as they do good, as they are ordinarily administered." F. Peterson has reported 11 cases in which the number of attacks was greatly reduced by withdrawal or marked reduction of the drug: "in some cases," says this neurologist, "the improvement is startling." Spitzka also wrote, long ago: "To give the bromides alone is to postpone the explosions and generally intensify them. The very fact that a sudden suppression of bromide administration is followed by a severe explosion is clear evidence that the drug acts rather like a load keeping down a safety valve." C. E. DE M. S.]

The full depressing action is not obtained from a single large dose, but only by keeping the body saturated with the drug by means of moderate daily doses, such as 15 to 20 grains (1 to 1.3 Gm.) morning and evening. In obstinate cases the dosage is progressively increased until the convulsive attacks are brought under control or symptoms of chronic intoxication appear. Potassium bromide is the most efficient single bromide, though a mixture of several salts, *e.g.*, potassium and ammonium, or potassium, sodium, and ammonium bromides, is preferred by many. By greatly decreasing the amount of sodium chloride in the diet of epileptics, it is found that the daily dose of bromide required to saturate the system with it can be lessened, the tissues taking up the bromide all the

more readily owing to their lack of sodium chloride.

In **chorea** and **hysterical spasms** bromides are also useful, though not of special importance, as in epilepsy. In **delirium tremens** and other forms of delirium they may be used to assist the action of the stronger hypnotics.

As spinal and medullary depressants the bromides are extensively used. In **spinal convulsions**, **tetanus**, and **strychnine poisoning** and other convulsive disorders, bromides are given in large doses to depress the sensory spinal centers, but large doses, such as 2 to 4 drams (8 to 16 Gm.), are necessary to obtain the spinal effect in these cases. If combined with chloral, which depresses the motor side of the cord, a maximum degree of spinal depression is obtained. Ammonium bromide should be avoided in these conditions, as the ammonium in large doses is a spinal stimulant.

In **nervous conditions** related to the **genital organs**, including the reflex nervous symptoms succeeding upon the **menopause** and in **uterine disorders**, also in the case of **excessive seminal losses** in the male, bromides are of value as spinal sedatives.

In other reflex disturbances, such as **whooping-cough** and **vomiting of pregnancy** or **seasickness**, bromides are also useful, preventing sensory irritation from causing motor response.

In affections with severe **itching** which is not controlled by local applications, bromides may also be used to depress the sensory centers and nerve-endings.

C. E. DE M. SAJOUS

. AND

L. T. DE M. SAJOUS,

Philadelphia.

BRONCHITIS, ACUTE, SUB-ACUTE, AND CHRONIC, and their various forms and complications.

DEFINITION.—Bronchitis is a catarrhal inflammation of the mucous membrane of the bronchial tubes, which may be **acute**, **subacute**, or **chronic**. These forms may in time lead to complications which have been termed **dry**, **purulent**, and **putrid bronchitis**, **bronchorrhea**, **emphysema**, **bronchiectasis**, and **pulmonary gangrene**.

SYMPTOMS.—Some cases of acute tracheobronchitis, or inflammation of the large bronchi and trachea, develop the mildest possible form of the disease, but other cases exhibit discomfort and even distress for one, two, or three weeks; however, it is never so great or serious as is capillary bronchitis.

In the mildest cases the only observable symptom is cough. On physical examination the respiratory sounds will be found slightly coarser than natural, and sometimes accompanied by fleeting or shifting râles.

In the moderately severe cases a feeling of chilliness or successive slight chills occurs for an hour or two. Then the patient feels hot and recognizes the existence of a fever which has been developing. Headache at this time is common, and general aching and lassitude are the rule. Sometimes sneezing and always coughing begins soon after the onset of the disease. Breathing may be slightly increased in rapidity by fever, and the heart may be quickened for the same reason. In many instances a feeling of rawness is felt behind the sternum when a deep breath is drawn. The nose and throat may or may not be simultaneously inflamed. It is rare that the temperature is high in adults, though in children it reaches 102.5° or 103° F.;

more frequently it ranges from 99.5° to 102° F. The second day the general muscular pains and lassitude continue, and coughing is more frequent and harder. The latter often causes muscular soreness about the waist, the epigastrium, and loins. After another twelve or twenty-four hours a small amount of vitreous adhesive mucus is expelled by the cough. It gradually becomes more abundant, thinner, less adhesive, and more frothy or purulent. When the sputum becomes abundant the abnormal temperature usually subsides, and with it general pains and lassitude disappear. The patient may still be weak, though no longer lacking in ambition. So long as the fever lasts appetite is diminished or capricious, thirst increased, and the bowels are inactive. The urine is often also somewhat diminished in quantity and dark in color.

When only the larger bronchi are inflamed no visible change is observable in respiration or in the appearance of the chest. Resonance is quite normal. Vocal fremitus is not increased and rarely is there a bronchial fremitus. The respiratory sounds are coarser than is natural and dry so long as the exudate is wanting or small in amount, but when it becomes abundant coarse, moist râles are either constantly or now and then audible. In severe cases the former condition prevails, and in mild cases the latter. When the trachea is exclusively or almost exclusively inflamed these changes in the respiratory sounds will be absent and a physical examination will reveal no positive signs of disease. Acute capillary bronchitis oftener begins with a well-marked chill than does the form just mentioned, and it is more frequently accompanied by noticeable fever. A frequent, dry and

hard cough develops almost at once. Indeed, cough, expectoration, and dyspnea may be considered the cardinal symptoms of the disease. To be sure, expectoration does not take place in infancy, old age, or among the very feeble. From the onset of the disease breathing gradually grows quicker, more labored, and productive of the subjective distress of dyspnea. In twenty-four or thirty-six hours and sometimes earlier the symptoms may become severe and life may be in danger. The face is then congested, the lips full and later livid. The nares expand with each inspiration. Breathing grows quicker and more labored. It is often noisy; expiration especially is prolonged and produces a wheeze. Patients are most comfortable when sitting erect or, if they are children, when held upright. The continuous labor of breathing and the frequent hard coughing are most wearisome and exhausting. Expectoration is usually scant during the first days and in the severest cases. What is raised looks like a small ball of white or cream-colored mucus, which frequently can be unrolled when dropped into water and will then appear like one of the mucous strings which can be drawn from the small bronchi at autopsy. Sometimes the larger bronchi are quite as much involved as the small ones, when a more abundant frothy expectorate will be formed earlier. The temperature of these patients is often high at night, from 101° to 103° F., but commonly normal, or nearly so, in the morning. The pulse is quick, and in dangerous cases grows quicker and weaker; the patient becomes very cyanotic, his skin cool and clammy, and lips and finger-nails purplish. He grows somnolent and nearly or quite unconscious. He lies quiet, too weary and

too dull to move. Respiration becomes shallower, less wheezing is heard, but a coarse rattle in the throat becomes more persistent and louder; coughing ceases or is infrequent and feeble. Expectoration ceases altogether. Life ebbs as the patient gradually suffocates because of inability to force air through the obstructed bronchioles.

Fortunately most cases of the disease are not fatal, and after four or five days of illness improvement is noticed. Coughing is less frequent and severe and accompanied by an expectorate which is more abundant and looser. The fever gradually lessens. Respiration is less hurried and difficult. Appetite, which has been almost wanting, returns. Strength and health are somewhat slowly regained. By severe attacks patients are much weakened and often lose much flesh. In mild cases nutrition is scarcely interfered with. Relapses are especially frequent in capillary bronchitis.

The chest will be seen to be enlarged from emphysema, and in the severe cases it is constantly in the position of extreme inspiration with the ribs widely separated. During inspiration, the whole chest is lifted by the unusual muscles of respiration, the lower intercostal spaces and abdomen are retracted in adults, and in children the lower ribs are also because of the low intrathoracic pressure. These changes vary in degree, as does the dyspnea, with the intensity of the attack. The frequency of respiration also varies in the same way. In childhood it is sometimes very rapid, as many as 60 respirations per minute. In adults it is much less hurried, 40 to 45 respirations being excessive. Children often feel pain on pressure in certain intercostal spaces and in small areas, usually where there

is catarrhal pneumonia and pleurisy. An abnormal vocal fremitus is not commonly felt, although it may be if pneumonic or atelectatic areas of considerable size happen to be developed. Resonance is usually normal or somewhat increased because of emphysema. It is always more extensive than is normal, because the liver and heart are depressed and the latter more extensively overlapped than is natural by the emphysematous borders of the lungs. On auscultation râles and rhonchi are heard, fine or coarse according as the large or the small bronchi only contain movable and bubbling secretions. Vesicular sounds are always wanting. Inspiration is short and coarse, expiration feeble and prolonged. In mild cases these modifications of the normal sounds are best heard over the lower and back part of the chest.

Whenever areas of consolidation develop of sufficient size the characteristic physical signs, dullness, increased fremitus, and bronchial breathing, can be detected. Extensive catarrhal pneumonia commonly increases fever, which will range at or above 103.5° F.

The writer finds that in children subject to **recurrent** bronchitis there is an underlying condition which is common to the difficult feeding cases, eczema, recurrent vomiting, and bilious attacks, and that these children are frequently the offspring of parents who suffer from disturbed metabolism. They frequently bear cow's milk and sugar badly, and exhibit a lessened resistance. It is apt to come on during cold months when the eliminative functions of the body are less active. It has been found that 41 per cent. of the cases of recurrent vomiting suffer from recurrent colds. A diet having an excess of fats and carbohydrates seems responsible for recurrent bronchitis in chil-

dren. When the carbohydrate content of the diet is cut down in such cases marked improvement usually ensues. C. G. Kerley (*Med. Rec.*, May 30, 1914).

In mild cases of capillary bronchitis the physical signs, as would be expected, are much less pronounced.

CHRONIC AND SUBACUTE BRONCHITIS.

Bronchitis may be chronic from the start or grow out of an acute attack. Several acute attacks at intervals of several months or of one or two years may precede the development of the characteristic picture of chronic bronchitis. Subacute bronchitis displays a mixture of the phenomena of the acute and chronic disease. It usually lasts many weeks. Chronic bronchitis may last ten or twenty years or even longer. Unless complicated by bronchiectasis or other diseases or infections it is rarely fatal. It may be mild and scarcely interfere with general health, or, making one a chronic invalid, it may cause distress and confine one to the house for months at a time. Chronic bronchitis is one of the commonest diseases.

As just explained, the anatomical changes wrought by the disease are numerous; therefore, the symptoms are complicated and, as they occur in various combinations, give to the disease a variety of aspects or forms. Nevertheless, certain symptoms or conditions are common to most of them.

Chronic bronchitis runs an afebrile course except when complicated. The purulent and fetid forms develop a fever of hectic type.

The pulse is normal in rate and quality except in the forms of the disease just mentioned. When there is much chronic emphysema or peribronchitis and, consequently, much cirrhotic lung-

tissue, the heart is quickly excited by physical exertion, even by slight grades of it. Under these same circumstances the heart may hypertrophy because of the increased work which it performs in overcoming obstructions to the circulation through the lungs. The right side of the heart has the most work to perform and undergoes, relatively, the greatest change in size.

Appetite and digestion are often not impaired, though the former is usually lessened during exacerbation and when the disease is severe. Vomiting sometimes is provoked by severe and prolonged coughing, although there is no digestive disorder. Eating sometimes provokes coughing by irritating the pharynx. Loss of flesh does not take place except in the febrile forms of the disease, or during a severe exacerbation in its course, when appetite may be sufficiently impaired to cause a moderate loss of flesh. The physiologic activity of the kidneys is normal, and menstruation is not changed.

Pain is rarely felt as a result of bronchitis; even the substernal rawness or pain, so often felt in acute bronchitis, is uncommon. The muscles involved in coughing and in labored breathing become strong enough to do the work which they are called upon to do with ease and comparative comfort. Often the recti abdominales, muscles used in violent coughing, and the sternocleidomastoids, used in breathing when there is dyspnea, undergo hypertrophy.

More or less dyspnea is present in chronic bronchitis. In the mildest cases it is slight and only felt on considerable exertion, but it usually grows progressively worse as the disease grows worse. The rate of respiration is normal except when fever and complications quicken it, but it is usually quickened

more by exertion than it would be in health.

Coughing is a constant symptom of chronic bronchitis. It may cease for weeks or months in the mildest cases, but is usually noticeable almost daily. It is variable in frequency and severity from time to time, and it is often paroxysmal in character. The expectorate varies greatly in amount and character. Its changes are especially typical of the different forms or varieties of chronic bronchitis. Commonly five of these are recognized. The first is simple chronic bronchitis, or winter cough. In this group of cases fall the mildest, as well as some of the severe, although always the least dangerous.

Usually the disease starts as an acute or subacute bronchitis which recurs for several or many winters successively. In the summer there is apparently complete recovery. But as the winter attacks succeed each other they are apt to last longer and to disappear less perfectly in summer. Later on coughing persists into and through the summer, though not severe. Thus gradually all of the phenomena of the disease, coughing, expectoration, and dyspnea, become persistent throughout the year, though varying in severity from time to time. Exacerbations are especially bad in winter and early spring. Coughing is usually hardest in the morning, when secretions which have accumulated over night must be expelled. Exertion sometimes provokes it, as does also a change from a cool to a hot, or from hot to a cool, air.

The expectorate varies from a trifling to a large quantity of frothy mucus, and from a glairy, tenacious mucus to a frothy seromucus or mucopus.

Dry Bronchitis.—In this, the second form of chronic bronchitis, the

coughing is usually more severe and paroxysmal and no expectoration takes place, or rarely a little viscid tenacious mucus is expelled. The mucus in the bronchi is increased slightly, but is so thick and adhesive that it cannot be expelled by coughing.

Bronchorrhea.—In this, the third form, bronchiectasis (treated at length below) is always present. The expectorate is large in quantity, sometimes amounting to several pounds in a day. It is serous in character and expelled periodically, and often at very regular intervals. This is due to the fact that the serous fluid accumulated in the dilated bronchi is only expelled when a certain amount has gathered. Only in cavities such as are formed by dilated bronchi can such large quantities of fluid accumulate.

Purulent Chronic Bronchitis.—This represents the fourth variety. In these cases liquid pus similar to that found in an abscess is expectorated. This is due to ulceration in dilated bronchi, and, like bronchorrhea, may be regarded quite as much as a variety of bronchiectasis as of bronchitis. A hectic fever is the rule in these cases, the fever, however, being lowest when the expectorate is most abundant or, at least, most perfectly expelled. Emaciation takes place gradually, and death is usually caused by the progressive loss of strength incident to chronic fever. Sometimes a fatal result is hastened by the development of pulmonary gangrene as a complication.

A study of the numerous cases of purulent bronchitis which have arisen at one of the bases in Northern France during the winter of 1916-17 showed that the writers were dealing with an epidemic of a variety of

purulent bronchitis due to the influenza bacillus. It is almost constantly found in the sputum and in the pus of the affected bronchioles. In some typical cases it occurs apart from the presence of any other organism. Treatment has so far been unsatisfactory. Hammond, Rolland and Shore (Lancet, July 14, 1917).

The writers made careful bacteriological investigations of the sputum, blood, lung, and other tissues in a small group of unselected cases of the very fatal and somewhat epidemic purulent bronchitis of soldiers. While several organisms were isolated in some cases, the one constant feature was the presence of the influenza bacillus along with *Pneumococcus lanceolatus*. The latter organism was of low virulence for animals when first isolated but became extremely virulent after one animal passage. From these observations the authors suggest that purulent bronchitis begins as an influenzal infection, upon which a pneumococcal infection is engrafted and the latter causes the fatal termination by severe toxemia. Abrahams, Hallows, Eyre and French (Lancet, Sept. 8, 1917).

Putrid Bronchitis.—This constitutes the fifth form. It may be a complication of either of the other varieties. It is characterized by an intensely fetid expectorate. This odor is due to the growth of certain molds in the secretions in the bronchial tubes. In the sputum small balls, varying in size from a pinhead to a pea, can be seen composed of fat crystals, bacteria, and intertwined threads formed by a mold. These are called mycotic plugs. Fever, usually of a hectic type, is present in this form of the disease. It also may finally be complicated by gangrene of the lungs.

[A sixth form might be recognized as **asthenic chronic bronchitis**. It is developed gradually, *i.e.*, irrespective of any acute attack, as a result of prolonged

elimination, through the bronchial mucosa, of toxic substances of various kinds. It is thus frequently observed in gouty subjects, an attack alternating in some cases with one of acute gout; it may succeed amenorrhea or alternate with attacks of eczema, urticaria, uremia, etc., all morbid processes connected with the elimination of toxic products of imperfect catabolism. It is frequently observed in old age—the so-called *senile bronchitis*, in which asthenia is the most prominent feature to be taken into account when therapeutic measures are to be instituted. Mitral disease and enlargement of the tracheobronchial glands are contributing conditions because of their causing interference with the return flow of blood from the bronchi. EDITORS.]

Report of 30 cases of bronchial spirochetosis, or hemorrhagic bronchitis, met with in a naval hospital. This disease was discovered by Castellani over 10 years ago. Its cause is the "*Spirocheta bronchialis*." The most striking symptom was hemoptysis. The disease is insidious in onset. The general condition is good, there is no fever and the chest signs are mild or absent. There may, however, be a mild apical bronchitis or slight congestion at the bases. Expectoration is profuse, mucopurulent, and blood-tinged. Cough is frequent, nocturnal, and severe.

The diagnosis should be made only with the microscope. The silver nitrate stain of Fontana, as modified by Tribondeau, is advised. The incubation period is about a month and exacerbations are frequent. The disease is very contagious. It probably originated from the influx of Asiatic soldiers and workmen in France. Contagion is probably through spores. Complications are pneumonia, broncho-pneumonia and pulmonary tuberculosis. H. Violle (Bull. de l'Acad. de Méd., June 6, 1918).

The physical signs of chronic bronchitis are variable, depending upon the variety with which one has to do and the distribution and kinds of lesions

developed in each case. Usually respiration is quickened by slight physical exertion. Because of emphysema, or peribronchitis, or both, the difference in the circumference of the chest in extreme expansion and exhalation is slight. Breathing is noticeably shallow and dyspneic in character. As dyspnea develops slowly over a long period of time, the sufferer becomes accustomed to it, and it causes little distress as compared to that felt by one who has acute dyspnea. For the same reason tissue changes adapt themselves to the lessened supply of oxygen, and, therefore, dyspnea must be very great before cyanosis is observable. Thoracic resonance may be normal in mild cases, but is usually more extensive than normal and somewhat increased because of emphysema. But when the lungs are contracted and consolidated by considerable masses of peribronchial connective tissue, areas of dullness may be detectable and other signs of local consolidation. When there is bronchiectasis the physical signs of a cavity or of several may be discovered. In the mildest forms of chronic bronchitis the respiratory sounds are exaggerated, and here and there moist râles may be detected or at times may be present constantly. In somewhat more severe cases an expiratory sound will be heard constantly, growing longer usually as the smaller bronchioles become involved. Vesicular sounds are absent or obscured by râles. When the smaller tubes are much involved, breathing is often noisy because a constant whistling or crowing noise is produced in the bronchi. Except in the rare cases in which the lungs become extensively cirrhotic because of peribronchitis, a uniform distribution of physical signs over all parts of the chest is the rule

or, at least, a symmetrical distribution of them.

DIAGNOSIS.—A diagnosis of acute bronchitis is rarely difficult and is not apt to be mistaken for anything else. But it is not always easy to decide whether one has to do with a specific or non-specific bronchitis. Acute tuberculous bronchitis can sometimes be distinguished from simple bronchitis only by a microscopical examination of the sputum, but usually it is less diffused, the physical signs being limited to or concentrated in the apices. Whooping-cough, measles, and small-pox can only be distinguished by the development of new and characteristic symptoms in their course.

The following test recommended to differentiate tuberculosis and bronchitis: To 5 c.c. of a 24-hour specimen of sputum, add 20 c.c. of normal saline and 5 or 6 drops of acetic acid. Shake thoroughly and filter. Test the filtrate by boiling or with nitric acid for albumin. In 57 cases of chronic bronchitis this albumin test was invariably negative. Of 73 cases of suspected tuberculosis without definite signs about 87 per cent. gave a positive reaction, and probably 60 per cent. of these showed organisms within 2 or 3 months. Of 71 cases of clinical tuberculosis, 79 per cent. showed albumin if the sputum was taken during an elevation of temperature. In about 98 per cent. of 42 cases of proved tuberculosis, the albumin test was positive at some period in the course of the disease. Cornell (Bull. Can. Army Med. Corps, June, 1918).

The symptoms of acute capillary bronchitis are so characteristic that there is rarely difficulty in recognizing it. A first attack of asthma may be confounded with it, but the sudden onset, absence of fever, and short duration with rather sudden cessation usually make the latter easy of recognition.

The bronchial asthma, which is often due to uremia, is much more apt to be confounded with it. However, a thorough examination of the urine and history of the illness will make a diagnosis possible. Bronchitis due to passive congestion caused by myo- or endo- carditis and cardiac weakness is also sometimes mistaken for simple bronchitis.

It is impossible to draw a hard and fast line between cases of severe capillary bronchitis and catarrhal pneumonia, because the latter is associated with most cases of the former. Physical signs of consolidation of the lungs in patches are detectable only in the severest cases, and not always then, though pneumonia exists in many minute areas. Some clinicians have empirically established a line which denotes severity of infection rather than a pathological distinction. This consists in classifying all cases as capillary bronchitis with temperature below 103° F., and all as catarrhal pneumonia with temperature of 103.5° F. or over.

The febrile types of the disease suggest tuberculosis, but the absence of tubercle bacilli in the sputum and of a cutaneous or conjunctival reaction, and the symmetrical and uniform distribution of physical signs, prove that it does not exist.

ETIOLOGY.—All forms of bronchitis are caused by the same agents or conditions. The inhalation of irritating gases and dusts will excite bronchitis, but after it is excited some of the microbes constantly present in the upper air passages invade the raw or congested mucous membrane and cause a mild infection. It is questionable whether dusts do not usually carry organisms which are the chief cause of the disease. Certainly vegetable and animal dusts do, and these are the most

irritating kinds. As a rule, bronchitis is caused by infections. Specific infections such as tuberculosis, measles, whooping-cough, and small-pox are well-known causes of it. However, the cases commonly spoken of as bronchitis are due to non-specific infections, that is, they are due to various infectious agents such as streptococci, staphylococci, pneumococci, or others. Moreover, the bronchitis is not accompanied by a syndrome which is peculiar to infection by either one of these microbes. They are almost constantly in the nares, pharynx, and mouth of people, but provoke inflammation there or in the bronchi only occasionally. This explains why many attacks of bronchitis are preceded or accompanied by coryza, or pharyngitis, or both. Moreover, it is evident that other conditions are requisite to excite these catarrhal inflammations than the presence of the microbes on the mucous membranes. In other words, in addition to an exciting cause, that is, one of these infections, predisposing conditions play a considerable part in producing the disease. Cardiac diseases which lead to passive congestion of the lungs predispose to bronchitis. Anemia, rheumatism, Bright's disease, diabetes, and other debilitating states also commonly help to produce attacks. During convalescence from other diseases or from surgical operations vitality is lowered so that the ever-present microbes may successfully invade the tissues and excite inflammation as they could not in conditions of health. Enervating habits are especially frequent conditions which increase susceptibility to bronchitis. A life of confinement in poorly ventilated rooms greatly increases one's susceptibility because it necessitates breathing a foul and germ-laden air by one weak-

ened by confinement and by one especially who imperfectly ventilates his lungs, since he is not stimulated by exercise or fresh air to breathe deeply. Those who are for many hours in winter confined in rooms in which artificial heat has made the air dry and hot must daily go out into a cold and moist air, thereby experiencing an atmospheric change greater than weather changes ever produce. In this way not infrequently colds are contracted. Overheating by bodily exercise or labor, followed by sudden cooling, especially if one is greatly wearied or exhausted, also leads to the production of catarrhal inflammation of the air passages. The breathing of cold air does not produce the trouble, nor does cold upon the surface of the body cause it, as has repeatedly been demonstrated by experiments and by the experience of travelers in arctic regions. The air passages must be filled with the disease-provoking germs in order that the characteristic lesions be produced. Esquimaux may be free from coryza and bronchitis, but are very sure to contract it when they visit ships which contain the infectious dusts. Arctic travelers from civilized lands may be exempt until the dust beneath carpets or rugs is disturbed, when they, too, will have it. Extreme cold lessens one's vitality, and sudden changes from heat to cold especially do so.

Since of atmospheric changes which lead to bronchitis a sudden and considerable fall in temperature in a moist air *is the commonest*, we expect to find the disease most frequently in the temperate zones, and least in the tropics, and infrequently in the dry cold of the far North and South, except as sudden atmospheric changes are caused artificially by dwelling in close, badly ven-

tilated, and often overheated huts. And this is the fact. Moreover, a fall of temperature of a few degrees in a moist air is much more keenly felt and depressing than a much greater one in a dry air. Therefore, those living in the elevated and dry regions of the globe are less liable to catarrhal inflammations of the bronchi and upper air passages than those in cold, damp regions.

These atmospheric conditions exist oftenest in the spring and fall, though not infrequently throughout the winter. It is, therefore, especially in these seasons that bronchitis is common. It is relatively not common in years in which the summers are cold and damp and, therefore, the seasonal changes are least marked.

The constant use of alcoholic beverages, and especially the excessive use of them, increases susceptibility to colds. It also lessens one's power to resist infection. The excessive use leads to much debility, both directly and indirectly, by lessening appetite and disturbing digestion, and may lead to exposure to cold, wet, and various hardships because the drunkard does not realize what he is doing or where he is. Certain occupations especially predispose to bronchitis. Many who are employed in foundries, boiler rooms, and gas-houses must inhale irritating gases as well as be exposed to great changes of temperature. Grainsifters, coalminers, and stonecutters are exposed to the inhalation of irritating dusts day after day and for many hours each day. They are especially prone to chronic bronchitis. I have already referred to the ill effects of exhausting work in close rooms, conditions which exist in many factories and offices.

Rheumatism, gout, scrofulosis, and diabetes also predispose to bronchitis,

but of all diseases bronchitis more than any other predisposes to repeated attacks. Sometimes this may be due to a persistent infection of the bronchi, such as so commonly exists in mouth, nose, and pharynx, but this rarely occurs, if recovery is complete, because all investigations show that the healthy bronchi are almost uniformly free from micro-organisms, though they can be easily infected when an air loaded with them is breathed.

Many times catarrhal inflammation of nose, pharynx, or larynx causes bronchitis by direct extension from it, but in many instances bronchitis is not preceded or associated with any of these diseases. Chronic bronchitis often develops in those who have chronic nasal catarrh or infection of sinuses about the nose. The causal relationship of these latter to some cases of bronchitis is shown by the frequent amelioration and sometimes by recovery from it when they are cured.

Broncho-oidiosis refers to the various types of bronchitis and broncho-alveolitis due to fungi, occurring in the tropics. The symptoms are somewhat similar whatever fungus is the cause. In mild cases there is slight bronchitis with mucopurulent expectoration in which the fungi are found, while in severe cases the patient presents all the symptoms of phthisis with high hectic fever and hemorrhagic expectoration. The infection may take place from man to man and also probably by the fungi living saprophytically in Nature.

The diagnosis is based on the sputum findings. Cultural methods are necessary to identify the fungi. All the species of *Monilia* grow fairly well on gelatin. A. Castellani (Jour. of Trop. Med. and Hyg., Apr. 1, 1913).

The writer attributes the following disorders to spirochetes: syphilis,

yaws, relapsing fever, Weil's disease, Castellani's bronchitis, Vincent's angina, pyorrhea alveolaris, venereal warts, balanitis, ulcer tropicum, various gangrenous processes, abscesses and suppurations, enteritis colitis, dysentery. The pathogenicity of the spirochete in a number of diseases has not been proved. Van Beneden likens them to criminals who have never been caught with the goods. Castellani was not the first to find spirochetes in the sputum of certain bronchitides, but first described the full disease picture in 1907 in Ceylon. Since that period it has been recognized in other hot countries in Asia and Africa and also in Europe and the United States, chiefly in association with gangrene of the lungs, the spirochete being associated with fusiform bacilli as in Vincent's disease. There is little doubt that the affection has a world-wide incidence. The *Spirocheta bronchialis* possesses well-defined characteristics. It may occur in the mouth as a saprophyte, and has no connection with other spirochetic diseases like Vincent's angina and pyorrhea. The organism appears to be activated when an individual has been exposed to cold. During convalescence they vanish from the sputum. There are acute and chronic forms of bronchitis and if the former does not terminate favorably by crisis it may become chronic. A microscopic examination is essential to diagnosis. Arsenic in its various forms has power over the disease. Galli-Valerio (Corresp. bl. f. schweizer Aerzte, Feb. 10, 1917).

The writer found a number of cases of broncho-spirochetosis in France in 1916, first discovered by Castellani in 1905. At Toulon a comparatively large number of cases occurred among native troops from the Far East, and also in Europeans. The symptoms observed by the author in France were: Hemoptysis, the case generally having been diagnosed as tuberculosis, and the expectoration being of a peculiar vivid pink; and

frequent cough, worse at night. Physical examination of the chest often revealed little or nothing; in some cases there were signs of bronchitis with or without emphysema, or signs of consolidation. The general condition of the patient was often good, and frequently there was no fever. There may be a slight degree of anemia in such cases but the number of leucocytes is normal, as is also the leucocyte formula. Microscopical examination of sputum reveals enormous numbers of the *Spirocheta bronchialis*, an organism which varies in length, shape, and number of spirals. The length may be from 4 to 30 microns, and is usually from 7 to 14. According to Fantham, the medium forms are derived from long ones by transverse division. Certain of the spirochetes have very few spirals; others have a large number very close together. This spirochete has not yet been cultivated. The author has not been able to reproduce the disease in rabbits, guinea-pigs or pigeons, but Chalmers and O'Farrell have done so in a monkey by intratracheal injections. The disease is very contagious, probably by means of "coccoid bodies" derived from the spirochetes. The author believes that this spirochete may be present in small numbers in many individuals, as is the case with the pneumococcus, and that with lowered vitality of the tissues they may multiply and invade the whole of the bronchopulmonary system. Diagnosis is based on finding the *S. bronchialis* in the expectoration in the absence of the tubercle bacillus, of hyphomycetes and of ova of *Paragonimus westermanii*, Kerbert. Clinically, if a patient exhibits bloody expectoration of a vivid pink color and is in good health, broncho-spirochetosis should be suspected. Cases of mixed infection occasionally occur. Prognosis, as a rule, is favorable. Symptoms may disappear in three to four weeks. Relapses seem to be frequent, and chronic forms occur with mucopurulent, greenish, or bloody expectora-

tion. In many cases, rest, nourishing diet, and country air effect a cure. Ergotine and tincture of iodine, a few drops well diluted, may be given if hemoptysis is severe; and if there is much secretion and cough is painful, opium preparations. Arsenic and tartar emetic and arsenobenzol have been used in treatment and may be indicated in chronic cases. The possibility of this disease should be remembered in cases of hemoptysis. H. Violle (Lancet, Dec. 7, 1918).

PATHOLOGY.—Often only portions of the bronchi are affected at one time or are chiefly affected; for instance, in the milder cases only the trachea and the bronchial branches of it are involved, and in other cases the whole bronchial system may be; but the inflammation of the smallest tubes produces the greatest disturbances of function.

When the bronchial mucous membrane becomes inflamed the submucosa becomes congested and infiltrated with serum, which makes it swollen, and simultaneously the basement membrane is thickened and the epithelial cells are loosened. In mild attacks the histological changes may not extend beyond this, but in the severer ones the deeper tissues also are infiltrated with leucocytes, most abundantly about the blood-vessels. The deeper or outermost layers of the bronchial wall become swollen from congestion and infiltration with serum and leucocytes. The ciliated columnar epithelial cells, already loosened, are detached in patches exposing rounded embryonic ones. Among these, leucocytes are intermingled, and when later they become fatty form pus-cells. Although the mucous membrane is thus denuded, true ulceration almost never occurs. When the

cause of inflammation is removed resolution takes place, the cells and serum are reabsorbed, new ciliated epithelial cells are formed, and the tissues once more are normal in structure.

Usually the bronchi are affected more in certain areas than others, although affected somewhat diffusely. Therefore, although reddened by congestion, after death this deepened color may show only in spots. At first the mucous surface is drier than natural and has a dull gloss, but soon it is covered with an excess of glairy mucus. And when the exudate is considerable it makes the mucus thinner by the admixture of serum and white because of the presence of leucocytes or, later, yellow because of pus-cells.

The bronchial lymph-glands are usually swollen and often congested. The exterior of the lungs may not be abnormal in any way. If a lung is cut open in which there are inflamed bronchi, more serum than is usual will flow from the cut surface or, at least, from the ends of the cut bronchi, and in severe cases mucus or mucopus will protrude from them or can be squeezed from the smaller ones in the form of short strings.

When only the trachea and larger bronchi are involved the swelling of their walls does not materially narrow their caliber. Even the mucus and mucopus rarely interfere materially with respiration. But when the smaller bronchi are involved the deep infolding of the mucous membrane causes a considerable obstruction to respiration when it is swollen, and the mucus or pus and detached epithelial cells often completely obstruct many of the bronchioles.

Dyspnea, therefore, is a prominent feature of bronchitis involving the

smaller tubes. When a terminal bronchus is thus obstructed, either inflammation extends to the alveoli beyond, causing them to fill with desquamated cells and serum from their surfaces, or the air in them is absorbed and they collapse. Moreover, through the comparatively thin walls of the bronchioles the inflammation extends to the adjoining alveoli and causes their consolidation. Thus, minute areas of catarrhal pneumonia or of atelectasis are produced, but they only become sufficiently numerous or extensive to modify the clinical picture in the severest cases.

In capillary bronchitis emphysema is much more extensive than either of the changes just mentioned because inspiration is a more powerful act than expiration, the former being produced by strong muscles and the latter chiefly by the elasticity of the lungs and the weight of the thoracic walls and abdomen. It is easy to understand how, when bronchioles are only partly obstructed, as are most of them in capillary bronchitis, air will enter and distend the alveoli, but will be imperfectly emptied from them; therefore, the lungs will gradually become more and more distended or emphysematous. All of these pulmonary complications or associated lesions of capillary bronchitis increase dyspnea.

The heart in these cases is often dilated, especially on the right side, and in chronic cases both dilated and hypertrophied. Just before death from capillary bronchitis edema of the lungs often develops, the cardiac changes just mentioned making it particularly liable to develop.

The anatomical and functional disturbances which have been described as characteristic of acute bronchitis

vary greatly in severity. Often they are slight, trivial, and transitory. But they may be great, dangerous to life, and persistent.

The anatomical changes which occur in the bronchial tubes in chronic bronchitis are numerous, and occur in various combinations in different branches of the bronchial system and in different cases of the disease. In acute exacerbations the phenomena of acute bronchitis will be found mingled with those of chronic bronchitis.

The mucous membrane is often gray or brownish red in places. Frequently it is thickened, and sometimes even papillomatous growths develop from it. Occasionally it is thin, and in dilated bronchi may look more like a serous than like a mucous covering. The connective tissues are, for the most part, hypertrophied, and invade the muscular layers. The latter are commonly atrophied, as may be also the cartilages, except when they have been calcified in old age. The bundles of elastic fibers may remain unchanged or be hypertrophied. Because of these last changes sometimes the interior of a bronchus appears divided by ridges, the latter due to the thickened bundles or bands of elastic fibers and the depressions to the atrophied muscular tissue. Abrasions of the mucous membrane are numerous and often extensive. Ulceration is not uncommon, but is most frequently observed in dilated bronchi.

Peribronchitis is the rule. It makes the walls of the large and small bronchi much thicker, and because of it the latter sometimes seem imbedded in a mass of connective tissue. The adjoining alveoli are destroyed and nearby ones often deformed and their walls greatly thickened and their elasticity

destroyed, causing them to fill with desquamated cells and serum, or the air in them is absorbed and they collapse. Moreover, through the comparatively thin walls of the bronchioles the inflammation often extends to the adjoining alveoli and causes their consolidation.

Bronchiectasis is common. More or less emphysema is always present.

The content of the bronchial tubes varies from time to time and in different cases. Sometimes it scarcely seems abnormal; at others it consists of adhesive vitreous mucus, and oftener of frothy and more liquid mucus. Mucopus is very commonly formed in them. Bronchiectases may contain a serous liquid or pus.

PROPHYLAXIS.—Prevention of bronchitis will be accomplished when the danger of stale air and air heavily laden with dust is fully appreciated and its inhalation prevented. Those prone to bronchitis should not follow occupations which expose them to irritating dusts, and others who must work in them should wear respirators which will filter the dust out of the air breathed. Air in offices, factories, public conveyances, halls, and elsewhere should not be allowed to become stale. This can be accomplished by good ventilation, which means not only the removal of the air rapidly enough so that those who breathe it will have a feeling of well-being, but, at least at intervals, vigorously enough so that pathogenic organisms will be removed.

It is a great mistake in the winter season to live in a house which is heated above 70° F. Indeed, two degrees lower is better, and at night a much lower temperature is to be preferred. If these temperatures are maintained by indoor workers, they will feel the changes out of doors much less.

Moreover, at these temperatures room air is not so likely to become excessively dry. Of late it has become a fad with many to sleep out of doors at all seasons. This insures filling the lungs perfectly for many hours with pure air, and it certainly helps to prevent colds of all kinds.

Clothing must be worn and must protect the body so that sudden changes of temperature will be as little felt as possible. This is best accomplished by wearing wool or silk next to the skin, although those who are leading an active life can wear with comfort linen coarsely woven.

Enervating habits must be corrected by those prone to bronchitis or wishing to avoid attacks.

Chronic catarrhal diseases of the nose, adjacent sinuses, pharynx, and larynx must also be cured, since they predispose to bronchitis, and especially to recurrent attacks.

TREATMENT.—The mildest cases require no medicinal treatment. Such guidance as will prevent an aggravation of the disease and a few days are all that are needed.

In the treatment of bronchitis and bronchopneumonia in children the writer recommends as a prophylactic the instillation once daily into each nostril of 5 or 6 drops (0.30 or 0.36 c.c.) of a solution of oil of sweet almond, 40 Gm. (1½ ounces), containing 0.4 Gm. (6 grains) of menthol, and every now and again inserting into each nostril some ointment consisting of 0.3 Gm. (5 grains) of resorcin and 3 Gm. (48 grains) of boric acid in 30 Gm. (1 ounce) of petrolatum. This treatment is instituted with a view of promoting antisepsis of the nasal fossæ and nasopharynx. To disinfect the mouth the writer advises swabbing with a pledget of wool soaked in 1 per cent. solution of resorcin once or twice daily, and if stomatitis exists

the mouth should be cleansed once or twice daily with boiled water. Where cases of bronchitis or bronchopneumonia already exist in a hospital these should be isolated to prevent spread of infection to other patients. When bronchitis of the larger tubes is present, treatment should aim at rendering the bronchial tubes antiseptic, facilitating expectoration and calming the cough. Marfan (*Jour. méd. de Brux.*, May 2, 1907).

Oftentimes when coughing is hard and frequent, though the bronchitis is limited to the largest tubes, and especially when it causes muscular soreness in and about the chest, a few doses of an anodyne will lessen the frequency and severity of the cough and the bronchitis will shortly disappear. Codeine is the most eligible anodyne, as it is less likely to disturb appetite and digestion than morphine. It can be given to adults in doses of $\frac{1}{4}$ or $\frac{1}{3}$ grain (0.015 or 0.02 Gm.) three or four times daily, or morphine can be given instead in doses of $\frac{1}{10}$ to $\frac{1}{8}$ grain (0.006 to 0.008 Gm.) or heroin in doses of $\frac{1}{10}$ to $\frac{1}{20}$ grain (0.006 to 0.003 Gm.). Rarely even smaller doses of codeine or morphine given oftener so as to produce a more persistent effect are found more useful; for instance, $\frac{1}{6}$ or $\frac{1}{8}$ grain (0.01 or 0.008 Gm.) of codeine every hour and a half or two hours. These frequent doses are only used when coughing is very persistent and exhausting. Both drugs tend to constipate patients, which must be prevented by combining with them a laxative. Constipation and indigestion, with the foul tongue, congested pharynx and tonsils which commonly go with them, often prolong by helping to reinfect the bronchi or by producing a soil which is fertile, fill the mouth and pharynx with germs which, when inhaled, aggravate or pro-

long the disease. It is well at the beginning of an attack of bronchitis to empty the bowels thoroughly by **calomel** or a **saline**, or by both. Only small quantities of easily digested food should be permitted. It is usually best to give the anodynes just mentioned in a capsule, and combine with them in appropriate doses **rhamnus purshiana**, **aloes**, or **podophyllin**.

Infants are often given **sodium bromide** to lessen cough. It is not as efficacious as codeine, though safer. **Chloral** can be given to adults and older children with especial advantage when the cough is paroxysmal and severe. Often it is a useful adjuvant to codeine when coughing is aggravated at night. **Codeine** can then be given during the day, and a single dose or rarely two at night of **chloral** of 15 grains (1 Gm.) in simple syrup, or syrup of yerba santa, or licorice.

Before leaving this subject of anodynes in bronchitis a word must be said about the old-fashioned *abortive treatment*. Patients strong and vigorous when attacked can sometimes be so treated while in the stage of congestion as to prevent the disease progressing beyond this point. However, it is rarely possible to institute the treatment, as almost invariably a physician is called when the lesion is more advanced. Abortive treatment should be applied as the chills cease and as coughing begins, when the tissues involved are congested and irritated, but not yet filled with an exudate. The treatment consists in administering an opiate and provoking diaphoresis. **Dover's powder** in a dose of 10 grains (0.6 Gm.) is the preparation which is most eligible under the circumstances. A **hot bath, a hot drink, and immediately**

thereafter envelopment in blankets will provoke sweating. This tends to deplete the congested vessels, and the anodyne lessens the irritability of the affected tissue, so that if the blood-vessels have not yet lost their tone and the mucous membrane has not been greatly hurt by the exciting cause recovery takes place almost at once. Such treatment, however, is not effective in those who are weak or anemic at the time of attack. **Quinine** and **strychnine** to give vascular tone, and **morphine** to lessen irritability in the affected tissues, have been tried in these latter cases, but rarely with much success.

One of the best procedures *to increase the liquidity of exudates* and to make them easier of expulsion is the administration of **water** copiously and preferably **hot**. Other **hot drinks**, such as lemonade, tea, or cocoa, can be substituted in part for water, but are very apt to derange digestion if taken often. Next to water in degrees of efficacy and harmlessness must be placed **ammonium carbonate** and **chloride**. They are very moderately irritating to the stomach and do provoke more abundant and thinner secretions from the bronchial mucous membrane. They can be best given in capsules, though they are often prescribed dissolved in syrup. Syrup of licorice and syrup of yerba santa cover their disagreeable pungent taste fairly well. If given in capsules patients should be instructed to take them only after meals or with a copious drink of water, that there may be enough fluid in the stomach to dissolve them readily. Ammonium chloride deliquesces so readily that it cannot be given in capsules unless incorporated with something that will prevent it.

The nauseating *expectorants* are frequently given with an opiate, and sometimes with the preparations of ammonium just mentioned. In simple bronchitis they are not used to produce emesis, but to provoke copious secretions. As they must be used in moderate doses when not given as emetics, they are commonly used as adjuvants to the stimulating expectorants. **Tar-tar emetic, syrup of squills, and syrup of ipecac** are good examples of this class of drugs.

Although expectorants are especially indicated in the dry stage of bronchitis or when the expectorate is very adhesive, they are oftener prescribed and given from the beginning to the end of an attack of the disease. This is a mistake, for they tend to disturb digestion if given long, and thus they aggravate conditions which the disease produces. They should be given no longer than is required. When secretion becomes copious they can be stopped and only an anodyne given.

As I have already implied, in most cases of bronchitis of moderate severity an anodyne and an abundance of water at the right time are all that are needed for the conduct of a case, except appropriate attention to surroundings, diet, and ventilation.

The following formulæ will be found useful, and are eligible ways in which the drugs which have been mentioned can be administered:—

℞ *Ammonium carbonate* 0.3 Gm. (5 grs.).
Codeine,
Aloin of each 0.02 Gm. (½ gr.).
 For one capsule.
 Take 1 four times daily.

℞ *Guaiaicol carbonate* . 0.3 Gm. (5 grs.).
Codeine,
Aloin of each 0.015 Gm. (¼ gr.).
Strych. sulph. 0.001 Gm. (¼ gr.).
 For one capsule.
 Take 1 three or four times daily.

℞ *Ammonium chloride*. 10 Gm. (2½ drs.).
Morphine chloride .. 0.2 Gm. (3 grs.).
Antim. et pot. tar-
tratis 0.1 Gm. (1½ grs.).
Fl. rham. purs. 20 Gm. (5 drs.).
Syr. yerba santa,
 q. s. ad 120 Gm. (4 oz.).

Take 1 teaspoonful in water three or four times daily.

℞ *Tinct. sanguinaria* .. 10 Gm. (2½ drs.).
Tinct. opii camph.,
Syr. scilla comp.,
 of each 40 Gm. (10 drs.).
Syr. Tolut. 120 Gm. (4 oz.).

Take 1 teaspoonful in water four to six times daily.

Drugs which are excreted in the urine as alkalies are also used to make the secretions in the bronchial mucous membranes more liquid. These are **sodium bicarbonate, acetate and citrate of potassium, and ammonium**. When in some cases the kidneys are quite inactive, they can be used most appropriately because they are diuretics as well as expectorants.

In capillary bronchitis the symptom of greatest importance is dyspnea, not only because it distresses the patient, but because it exhausts him. Moreover, congestion of the bronchi and emphysema, or often atelectasis and pneumonia, impede the movement of blood through the lungs, and, therefore, tend to exhaust the heart, especially the right ventricle. The most important indication for treatment is, therefore, to relieve dyspnea by loosening the exudate in the bronchi and by expelling it from them or hastening its absorption. Paramount with this is the necessity of maintaining general and cardiac strength.

Children are greatly comforted because breathing is made easier by enveloping their chests in **hot poultices, Hot tub-baths**, at regular intervals, may be substituted for the poultices.

If either measure is adopted it is best to leave night clothing off, but to cover the patient warmly with blankets. The poultices should go entirely around the body and cover the chest perfectly. They must be changed often enough to keep them hot. An oil-silk dressing on the outside will help to retain the heat. The proprietary preparations made of clay, glycerin, and aromatic oils, used so much today, do not fill the place of the old-fashioned poultice of flaxseed or similar material. It is true the glycerin in them keeps them from drying, and they feel as hot as the patient's skin from which they derive heat, but they do not, unless changed with the same frequency and applied at the same temperature, produce the relief of dyspnea and apparently lessen the intensity of congestion that the poultice does. Moist heat is required. Counterirritants, such as sinapisms and dry heat, do not produce the same effect. Hot tub-baths, if used, must be repeated about every two hours. The bath should last for from five to ten minutes. The patient must be rapidly dried and put quickly in a warm bed. The baths require more exertion on the part of the patient than the application of poultices, and are wearying for that reason.

To make the secretion as little adhesive and, therefore, as easily dislodged as possible, patients should be encouraged to drink water freely and preferably hot water. The inhalation of a moist, warm air is also a great help. The room in which a severe case of capillary bronchitis is being treated should be kept at a temperature of 70° to 72° F., and the air well filled with moisture by having water evaporated constantly in it. At the same time the

utmost care must be taken to keep the air fresh and clean. In all except the severe cases it is best to let the outdoor air in freely, but temper it by heat. It will be, as a rule, much moister than house air. A temperature of 68° to 70° F. is sufficient, except when poultices or hot baths are used.

For the same purposes ammonium carbonate and chloride can be used as in simple bronchitis. The nauseant expectorants, such as ipecac, squills, tartar emetic, and apomorphine, can be given in small doses, but it must be remembered that they increase the patient's distaste for food and increase a tendency to vomit it, which the coughing due to the disease also often provokes. They, moreover, are depressing, especially if used in efficient doses. They can be given as in simple bronchitis. Apomorphine is best given in capsules in doses of $\frac{1}{20}$ grain (0.003 Gm.) every two to four hours. Rarely is it desirable to provoke vomiting for the purpose of emptying the air passages of the mucus in them. If a patient is strong, but very dyspneic and cyanotic, an emetic dose of the sub-sulphate of mercury can be given. It will promptly produce vomiting, and with the least general depression. Often in this way breathing can be temporarily greatly helped. This drug must not be given often, for it will then irritate the stomach and greatly depress the patient.

When a patient grows weary because of rapid and difficult breathing, the bronchi are emptied less perfectly of the secretion in them by coughing and by breathing. It is then desirable to stimulate these acts. Strychnine is the best respiratory stimulant. Often it must be given in full doses, as much as $\frac{1}{80}$ grain (0.002 Gm.) every

three hours or even two hours. An alternate shower of chest and back, with cold and hot water, will temporarily stimulate deep and forceful breathing. However, this is disagreeable to the patient, and of such temporary advantage that it is rarely resorted to, and then only in extreme cases. **Inhalation of oxygen** will often greatly lessen cyanosis and the feeling of distress which patients have. When used, oxygen should be given freely. Under its influence the blue lips and finger-nails may become pink, the patient's mind may seem more clear and all functions more normal, but it does not make breathing deeper or stronger, check the secretions accumulating in the bronchi, or aid in their expulsion. Therefore, in severe cases, in spite of the inhalation of oxygen, cyanosis returns. Nevertheless, it often contributes to the comfort of patients and sometimes tides them over critical hours.

In this disease **morphine** and other hypnotics should only be used in the mildest cases, and then as little as possible, because they lessen coughing and the depth of breathing, thus hastening the development of cyanosis or intensifying it. To be sure they may make a patient sleep when wearied, but this is **not always a benefit**. The greatest discretion must be exercised in their use, and in severe cases in which they may be craved they must not be used at all.

Congestion of the bronchioles and even of the lungs many times increases the tension of the pulmonary arteries and right ventricles, and, therefore, leads to heart weakness and dilatation. Moreover, the slight variation in intrathoracic pressure due to shallow breath-

ing and emphysema also hastens and increases venous congestion. When the heart is thus taxed and enfeebled its condition makes the congestion of bronchioles and lungs greater. Therefore, it is of importance to stimulate the heart when it flags. Diffusible stimulants, such as ammonium carbonate and camphor, are the best. The former is most effective when given in solution, because then the reflex stimulation produced by irritating the mouth and gullet is effective as well as the drug when absorbed and brought in contact with the central nervous system. A simple solution of **ammonium carbonate** in water or syrup, or the **aromatic spirits of ammonium**, may be used. These are also often needed at the same time as expectorants. Their effect as cardiac stimulants is very transitory. Therefore, they must be given often. **Camphor** can be administered hypodermically when dissolved in olive oil in about the proportion of 1 to 10. **Alcohol** has been used as a cardiac stimulant, but its effect is even more transitory and due almost, if not, exclusively to a reflex irritation of the gullet. If often repeated or given in considerable quantity it produces its anesthetic effect, and makes breathing slow and shallow, and the heart beat less forcefully. It is not, therefore, a good or reliable stimulant under these circumstances.

Cardiac tonics, such as **digitalis** and **strophanthus**, must be used when the pulse becomes quick and weak. Such usual therapeutic doses as 10 minims (0.6 c.c.) of the tincture, a $\frac{1}{4}$ grain (0.15 Gm.) of the extract of digitalis, or $\frac{1}{60}$ grain (0.001 Gm.) of **digitalin**, hypodermically, may be sufficient, but sometimes half or even twice as much is needed to be effective.

Veratrum and **aconite**, recommended a generation ago, must be used with great caution and only in the beginning of attacks to deplete the congested vessels. They are contraindicated if the heart is weak or if its enfeeblement is imminent. They are almost discarded today in the treatment of capillary bronchitis.

The writer found that 20 to 25 drops of the fluid extract of **hydrastis canadensis**, 3 times a day, is an excellent drug for bronchial catarrh, whether tubercular or not. Saenger (Münch. med. Woch., May 5, 1914).

In tracheitis or tracheal bronchitis the **bronchoscopic treatment**, permitting the direct application, on tampons, of **glycerite of tannic acid**, is ideal in the form with acute inflammation and profuse secretion of mucus, and should be practised every other day. In the form with crust development one should first remove the crusts and then touch the ulcerations with **silver nitrate** or other **silver salt**, or with a 10 per cent. alcoholic solution of **iodine**. Direct application of the **ultraviolet ray** also promotes absorption of inflammatory exudates and healing. R. F. Ridpath (Jour. Am. Med. Assoc., Jan. 27, 1917).

The writer treated 250 cases with **camphor**, with a mortality of 1—a man who died after 3 days' illness from broncho-pneumonia. The incidence of broncho-pneumonia in the 250 cases was 26, or 10 per cent.; in another series of 200 cases during the same outbreak, and untreated with camphor, the incidence was 8 per cent., but the number of deaths was 4, a mortality of $\frac{2}{3}$ per cent. The treatment adopted was the administration of pills containing 4 grains (0.26 Gm.) of camphor made up with soap, in mild cases 3 times daily and in the very acute cases every 3 hours. The treatment was continued until the temperature dropped and the signs of bronchitis or broncho-pneumonia cleared up. Giuseppe (Brit. Med. Jour., Dec. 28, 1918).

Sometimes when the heart is dilated and congestion is extreme **venesection** gives prompt and great relief. Its usefulness and these indications for its employment must not be forgotten.

Fever, though high for a few hours each day, rarely requires special treatment. **Fresh air** and **hydrotherapy** are the best means for its control if any are needed. Antipyretic drugs do harm because they lessen the oxygen-carrying power of the blood-corpuscles, thus increasing cyanosis, and lessen normal tissue change or nutrition and the activity of organs of elimination.

This is not true of the salicylates, at least to as great an extent. Many cases of subacute capillary bronchitis are seen in which the disease is a phase of a rheumatic diathesis, and they are greatly helped by antirheumatic remedies. **Sodium salicylate** may be given in doses of 15 grains (1 Gm.) or **acetyl-salicylic acid** in doses of 10 grains (0.6 Gm.) every four to six hours with benefit. The internal use of **ichthyol** is useful in subacute cases with profuse expectoration. The dose is 5 grains (0.3 Gm.) *t. i. d.*

The writer gave **hexamethylenamine** to 92 children with bronchitis and obtained appreciable benefit only in 5 of the 18 with acute bronchitis; in 8 of the 46 with subacute and in 2 of the 28 with chronic bronchitis. He concludes that it cannot be depended on in bronchitis in children, and that the hematuria and other by-effects sometimes noted by others, are the result of excessive dosage. Neves (Arch. de Méd. des Enfants, Jan., 1918).

The obtaining of the causal organism in a pure state for the purpose of preparing a **bronchitis vaccine** is often a matter which involves trouble and delay. The difficulty is largely due to the fact that the bronchial se-

cretion in its passage from the lung to the sputum-pot has necessarily passed through the mouth and become contaminated with the organisms which are the natural inhabitants of that cavity. These mouth organisms are often numerous, and more often than not present a much more luxuriant growth upon artificial media than do the lung microbes which it is the special object of the vaccine therapist to cultivate.

These adventitious microbes may be largely or entirely eliminated *ab initio* by making use of the following process.

An ordinary tea-strainer is sterilized in the flame, and in its wire-mesh cavity is placed a portion of the sputum from which it is desired to grow the offending organism. The strainer is then held under the tap and a stream of water allowed to impinge forcibly upon the sputum. As, however, the average watertap supplies too large a volume of fluid when much pressure is turned on, it is a good thing to fit the tap with a short rubber hose, the free end of which can either be fitted with a glass nozzle of reduced size or else constricted with the fingers in such a way as to diminish the volume and increase the force of the stream of water. The mechanical violence of the water will rapidly peel off and sweep through the meshes of the strainer the outward salivary wrappings of the sputum with the microbes contained therein, and this effect will also be contributed to by the superior solubility of the salivary portion to that of the more gelatinous bronchial mucus. This washing is continued until the greater part of the original mass has been driven through the strainer, and only true bronchial material remains behind. This remnant is then broken up with a sterile glass rod, and cultures are taken from its central parts with a platinum needle in the usual manner. W. E. M. Armstrong (Lancet, May 18, 1912).

Report of an epidemic of 418 cases of measles and rubella complicated

by purulent infection of the bronchi. Three different vaccines were used: (a) A mixed stock vaccine, consisting of 1250 million Pfeiffer's bacillus and 250 million Friedländer's bacillus per c.c. (b) A vaccine of *Streptococcus lanceolatus* and *Streptococcus pyogenes longus*. (c) A vaccine of *Staphylococcus aureus*, the pneumococcus, a streptococcus, and a Gram-negative bacillus. Vaccine A was given always in doses of 300 million Pfeiffer's and 60 million Friedländer's at intervals of 4 days. Vaccine B was usually given in doses of 25 million each. Of 36 treated with vaccine, 10 died, while of 25 untreated with vaccine, 16 died. The good results were seen in an improved general condition even more than in rapid subsidence of symptoms. MacDonald, Ritchie, Fox and White (Brit. Med. Jour., Nov. 2, 1918).

The strength of patients with capillary bronchitis must be maintained by **careful feeding**. The disinclination for food which the disease produces and the fever which accompanies it and the exhaustion caused by dyspnea and coughing produce loss of flesh and strength. Digestion is impaired, and too much food will cause distress. In planning the feeding of such patients it must not be forgotten that distention of the stomach or intestines or congestion of the liver will greatly interfere with breathing, which is made difficult enough by the trouble within the thorax. Therefore, the intestines should be emptied when treatment is first begun. This may be accomplished by a dose of **castor oil, calomel, or a saline cathartic**. Such a dose had best be repeated each day for two or three. That food may be well digested it should be given in moderate or small quantities, and, when least relished and dyspnea interferes with swallowing, in small quantities very frequently repeated.

Milk every one or two hours, **alone** or fortified with an egg beaten into it, is the best under these circumstances. Malted milk and similar preparations can be used as a substitute, or to give variety. Meat broths, though they contain little nourishment, often whet the appetite, and are unobjectionable if given occasionally, but should not be depended upon wholly. Eggs can be added to them, or somatose, or beef peptonoids, and the broths can thus be made more nutritious. Eggs, raw, soft, cooked, or made into custards, can also be recommended in all except the severest period of the illness. Gruels, if they do not cause flatulence, will also be found useful. Fruit juices, especially orange juice, are liked by patients, and can be taken with pleasure and benefit. During convalescence and in milder cases throughout the course of the disease, soft foods or finely divided solids can be eaten, and soon thereafter a variety of simply cooked solid foods. Care must be taken not to overfeed such patients, but enough must be given to prevent too rapid loss of flesh or exhaustion.

Regular movements of the bowels must be maintained throughout the illness.

During convalescence great care must be exercised to prevent exposure to cold, or an aggravation of the disease, or a relapse. **Warm clothing** is essential. **Fresh, clean air** is also essential. Overdoing often precipitates a relapse, and so does overheating or indiscreet eating.

After a severe attack, partly to avoid such exposure as might cause the disease to return, but chiefly to enable the invalid to get out of doors into the fresh air and sunshine, a **change of climate** is desirable. In midwinter the

best climatic conditions are found with greatest certainty in the southwestern part of this country between western Texas and southern California. Sunshine and at least in the daytime an agreeable temperature can be counted on in Arizona and much of New Mexico, and with a little less certainty in Texas and California. The Bahamas, the southern end of Florida, and the West Indies can also be counted on for a genial air, though one less stimulating than that of the more desert western land.

Those who have had at annual intervals several attacks should be taken to such climates as have just been described, for two or three winters, that they may outgrow the tendency to the disease which they have acquired.

Treatment of Chronic Bronchitis.—

In chronic bronchitis, to prevent exacerbations is the most important indication for treatment, because if they can be averted a genuine recovery may be effected or at least a comfortable existence. On the other hand, each exacerbation is likely to leave the patient permanently a little worse than before. To accomplish this object those suffering from chronic bronchitis must be shielded from inclement weather. To do this many must be housed during the winter and spring. Their health is usually thereby impaired, though they may escape severe attacks of bronchitis, and necessarily their usefulness is lessened. When housed it is essential that they shall not be exposed to infection by the *Bacillus tuberculosis*, which will readily invade those who have chronic bronchitis. Moreover, if when housed they must breathe dust-laden or gas-laden air, their disease will be aggravated. It is by all means better for these invalids to move to a **climate**

where they will be exposed to sudden and violent changes of weather as infrequently as possible. The milder cases often do well where the air in winter is dry and cold, provided they do not spend too much time in hot houses, especially if this is where the snow leaves the ground quickly in the spring and does not keep it wet for weeks, and consequently the air above it damp. Such climatic conditions can be found in many places in the Rocky Mountains. At altitudes of 3000 to 8000 feet the dry air quickly takes up moisture, and snow seems to almost evaporate into it rather than soak into the ground. In such a dry air cold is not felt so keenly as it is in one laden with moisture. Moreover, exudates are more rapidly removed from inflamed tissues in such a climate. In proportion as the air is rarefied it is stimulating and tonic in its qualities. However, those who are quite dyspneic are uncomfortable at such altitudes, for they cannot get oxygen enough into their lungs to satisfy them, and they must go to other climates at low altitudes. Moreover, those who are feeble and, therefore, not able to stand cold well will do better in a warmer climate. The last do well in the southwest, especially during the winter. Those of them who must seek a permanent residence find southern California or moderate elevations in New Mexico and Arizona best suited to their needs. Especially are those who have an excessive secretion of mucus or mucopus in their bronchi helped in this climate, for its dry air hastens the absorption of the secretions and prevents them, its equability lessens danger of exacerbations, and its continuous sunshine and warmth invites to a health-giving life out of doors. However, those who

have dry bronchitis or suffer from severe paroxysms of coughing accompanied by very moderate expectoration are usually more comfortable at the seashore or on the water, and during the winter in the tropics or semitropics. The moist, equable, and stimulating air of the ocean makes coughing easier and less frequent. Florida, the Bahamas, and West Indies are favorable places for them in winter.

Those who migrate in the winter from the North to more salubrious climates must be careful not to return too early in the spring. Therefore, they must often stay at intermediate points, such as Asheville or Hot Springs, Virginia, for a time.

Patients having chronic bronchitis should protect themselves by **warm clothing** at all seasons. Sometimes they need iron or other tonics to improve their general health so that they can become comparatively resistant. **Codliver oil** often helps children, and frequently is taken by them advantageously from fall to spring.

The so-called morning bath helps to accustom one to exposure to cold and wet, and makes one more resistant to them. This is, properly speaking, an exercise rather than a bath. The skin over the body should be momentarily chilled by emersion of the body in water at the temperature of the room or a little colder, or, what is better, subjected to a shower of the same temperature for a moment. This must be followed by vigorous rubbing with a coarse, dry towel so as to quickly make the skin pink and warm. The shower hastens this reaction because the fine jets pound the skin and excite in it a more vigorous circulation. The sudden contact of **cold water** with the skin causes for a moment deeper in-

spirations, and the exercise of rubbing maintains them. This mode of treatment is adapted to mild cases in periods of remission, but not to periods of exacerbation and rarely to severe cases. The following formula is useful in many cases:—

R Potassium iodide ... 10 Gm. ($2\frac{1}{2}$ drs.).
Potassium acetate .. 30 Gm. (1 oz.).
Syr. yerba santa,
 q. s. ad 120 Gm. (4 oz.).

Give 1 teaspoonful in water three or four times daily.

Three drugs, according to Auld, have a specific action on the epithelial and glandular tissues; they are **potassium iodide**, **balsam of Peru**, and **turpentine**. Of these the balsam of Peru is the most efficacious and the most generally applicable. When the expectoration is already free, balsam should be given in doses of 10 to 20 minims (0.6 to 1.25 c.c.), given disguised in an emulsion. If the expectoration is scanty and difficult to expel, begin with 5 to 8 grains (0.3 to 0.5 Gm.) of potassium iodide. Having obtained a free expectoration, this is followed up with the balsam of Peru.

To mitigate the discomforts which a severe cough accompanied by a scant expectoration causes, the **carbonate** and **chloride of ammonium** can be given or alkalies, such as the **acetate** or **citrate of potassium**. The latter are useful expectorants. They can be given in hot water or milk with increased advantage. The carbonate of ammonium can often be best given when the secretions are especially scant, in small, but frequently repeated doses. For instance, in doses of $2\frac{1}{2}$ grains (0.15 Gm.) every two hours. Especially in such cases is the cough apt to be severe and exhausting in the morning. A **hot nutritious drink**, such as milk or cocoa, and an alkaline expectorant given as soon as the patient awakes are particularly comforting. When coughing

is severe at night, and especially when a recumbent posture is taken, an anodyne may be required, such as a dose of **codeine**, or **morphine**, or, if the cough is very persistent and somewhat paroxysmal in character, **chloral**. It is best to give anodynes infrequently and only when symptoms are urgent, for the disease is so chronic that the habit of taking them is easily acquired. Moreover, they are apt to lessen appetite, produce constipation, and often disturb digestion. Therefore, a full dose given when it is most needed is better than to administer it more continuously.

The **iodide of potassium** or **sodium** is an efficient expectorant and often seems to stimulate the absorption of cellular and serous exudates from the tissues. It is also found useful in many of the cases of chronic bronchitis complicated by asthma. Occasionally it provokes a coryza, which increases the patient's discomfort. Many times iodides can be given advantageously for weeks or months. The sodium salt is then to be preferred because it is less irritating to the stomach.

At some sulphur springs bronchitis is treated by a stay of an hour or more each day in a room filled with the **vapor of the sulphur water**. The moist air makes coughing easier and less frequent, and the sulphur lessens the formation of mucus and pus and therefore expectoration.

Steam vapor is more frequently inhaled at home from an atomizer or steam inhaler. The addition of mild antiseptic, balsamic preparations lessens suppuration and the formation of mucus. Those most frequently employed are **tar**, **creosote**, **eucalyptol**, **turpentine**, and **benzoin**.

Such treatment is advantageous with indications already mentioned.

The same remedies are often given by the mouth, especially to change a purulent expectorate into a mucous one, or to diminish the quantity of an excessive expectorate, or to lessen its fetor. The most effective for the accomplishment of the two first indications is turpentine, and next in efficiency in about the order named are **copaiba**, **benzoin**, and **creosote**. For the last indication **creosote**, **guaiacol**, **eucalyptol**, and **turpentine** are to be preferred. Turpentine can be best given in emulsion, or in capsules, or in solution in syrup of Tolu. The dose is 5 minims (0.3 c.c.) or less four to six times daily. The tincture of benzoin is an eligible preparation for its administration. Guaiacol, creosote, and eucalyptus oil can be given in capsules most comfortably.

℞ *Ol. terebinthina* 10 Gm. (2½ drs.).
Syr. Tolutana 120 Gm. (4 oz.).

Give 1 teaspoonful in water three or four times daily.

Thirty capsules each to contain:—

℞ *Guaiacol* 0.3 Gm. (5 grs.).
Ext. grindel. rob. ... 0.2 Gm. (3 grs.).
Codeine,
Aloin of each 0.02 Gm. (⅓ gr.).

Take 1 four times daily.

Jennings has used **ichthyol** in many cases of chronic bronchitis in children and has had remarkable success. The following is found to be a good combination:—

℞ *Ichthyol* gr. xxxij (2.1 Gm.).
Glycerini,
Syrup aurantii,
āā 3ss (2 Gm.).
Aquæ ..q. s. ad ʒij (60 c.c.).

M. Sig.: One teaspoonful three times a day, after meals.

It is often found that the first dose nauseates, but later the child acquires a taste for ichthyol, although children under 1 year seldom take it well. It should be given after meals to avoid the disagreeable taste.

The excessive fetor of some sputa can be lessened by keeping the air in the bronchi filled with a volatile balsamic preparation, such as **eucalyptol**, or **creosote**, or **benzoin**. This is best accomplished by having the patient wear continuously, or, at least, most of the time, a respirator which will fit over his nose and mouth and strain all the air inhaled through cotton or porous cloth saturated with the antiseptic which may be chosen.

The writer has for several years made use of intramuscular injections of menthol and eucalyptol in the treatment of various bronchial and pulmonary conditions. He finds them very effective in bronchitis and gangrene of the lung, as well as in many cases of pulmonary tuberculosis. The formula generally used is as follows: Menthol, 10 Gm. (2½ drams); eucalyptol, 20 Gm. (5 drams); castor oil, 100 Gm. (3½ ounces). Menthol may also be given alone in the proportion of 1 part to 3 parts of castor oil. At first, injections of 2 c.c. (32 minims) of the solution are given three or four times weekly. Later the strength of the preparation is doubled and the number of injections reduced to two a week. The duration of the treatment naturally varies in different cases. In general, a course of injections covering four to eight weeks was found to give excellent results. Max Berliner (Berl. klin. Woch., May 23, 1910).

The writer recommends the distribution about the room, in which is a patient with chronic bronchitis and copious expectoration, of 5 or 6 pieces of filter paper which have been soaked in

℞ *Menthol*,
Eucalyptol āā ʒij (8 Gm.).
Oil of turpentine,
Spirit of juniper,
āā ʒv (20 Gm.).

M..

After a short time the abundant secretion dries up. Bulling (N. Y. Med. Jour., Dec. 30, 1911).

Adrenalin is invaluable in chronic bronchitis. It is least effective when inhaled; more effective, but only temporarily, when given subcutaneously, most lastingly effective when applied directly to the diseased bronchi. Ephraim (*Deut. med. Woch.*, Aug. 1, 1912).

The inhalation of compressed air and exhalation into rarefied air are resorted to seldom, for the necessary apparatus is not to be found everywhere, although it is most useful in selected cases. By means of the pneumatic cabinet or similar contrivances air is forced in and out of the bronchi forcefully, and the secretions in them dislodged and swept out. A patient in a **pneumatic cabinet** will often expectorate during a few minutes more than he ordinarily will in twenty-four hours or longer. This mode of treatment is also useful for the relief of emphysema. As just explained, it helps to remove the cause of emphysema, but also by subjecting the mucous membrane of the bronchi and lung-tissue to intermittent pressure it stimulates the absorption of exudates by the lymphatics. The distended alveoli are gradually emptied, and later forcefully filled and emptied, which helps to re-establish their natural elasticity. **Breathing exercises**, systematically and persistently carried on, help to accomplish the same results, but more slowly and less perfectly. And if emphysema is not too great a **residence in a rarefied air**, such as can be found at elevations of 4000 to 6000 feet, will help, because forceful breathing will be compulsory and the dry air will help to remove the liquid exudates within the bronchial tubes.

In bronchitis associated with cardiac insufficiency, the influence of the pneumatic cabinet, *i.e.*, of **compressed air**, is to promote the respiration; the diaphragm descends deeper, the lungs

expand, the walls of the bronchi spread apart, and the mucus clinging to them is carried out by the more vigorous respiration. The best results were obtained with chronic bronchial catarrh without much fluid secretion. Even with a weak heart musculature the blood-pressure does not drop in the cabinet, confirming the harmlessness of the method in uncomplicated cases of bronchitis in which cardiac insufficiency exists. Samter (*Berl. klin. Woch.*, May 20, 1910).

The writer has found **dry hot air** useful in simple chronic catarrhal inflammation of the larynx and bronchi; it is less effective in emphysema bronchitis and bronchiectasia, and is unreliable in tuberculous pulmonary and laryngeal processes. The patients inhale the superheated air through a tube with removable glass mouthpiece; the air is filtered through cotton, dried by passing through calcium chloride and heated in a small chamber inside a large asbestos-coated stove heated by gas or electricity. A thermometer is mounted in the tube near the mouth. The patients experience great relief from the dry hot air thus inhaled through the mouth and expelled through the nose and cure followed in many cases. Schmidt (*Therapie der Gegenwart*, Jan., 1911).

During periods of remission patients should be fed so as to maintain strength. It is not advantageous for patients to be burdened with flesh. Indeed, this condition makes breathing more difficult, coughing less effective, and the heart more easily weakened or exhausted. During exacerbations they must be fed as those having acute bronchitis. When there is hectic fever in purulent or putrid bronchitis food must be given as generously, but in as easily digested a form, as possible to sustain strength, which the fever is sapping. Such cases must be kept in bed, and, if possible, in fresh, cool; and clean air.

The treatment of chronic bronchitis taxes the skill of every clinician to the utmost. If the disease has not been of long standing and can be well treated, under favorable circumstances genuine recovery may be effected. Many cases can be kept from growing worse by good care. In few is it the immediate cause of death. Complications such as tuberculosis, pneumonia, and la grippe are easily superimposed upon bronchitis, and are then common causes of death. Purulent and fetid bronchitis are uncommon, but are usually fatal.

The writer found **arsenic** and potassium iodide extremely effectual in chronic bronchitis. He gives 2 drops of **Fowler's solution** 3 times a day on the first, third and fifth days, alternating it with a 5 per cent. solution of **potassium iodide**, of which a quarter of a teaspoonful is taken 3 times a day on the second, fourth and sixth days, and so on. Each of the drugs is taken in milk after meals. Wilcke (Med. Klinik, May 23, 1915).

Incandescent-light baths, by promoting diaphoresis and stimulating the bronchial glands, have been recommended in cases in which complications have not as yet arisen.

Kellogg's **incandescent-light baths** have first made it possible to induce energetic diaphoresis without the slightest inconvenience or annoyance to the patient. The writer has found this technique of the greatest benefit in chronic bronchitis, especially the dry form, without secretion. He warns expressly that it is suited only for the primary cases, and that they must be carefully differentiated for the purpose. Strümpell (Jour. Amer. Med. Assoc., from Med. Klinik, July 26, 1908).

The **X-rays** have been found efficacious in a number of cases, but the exposure must be carefully adjusted to the needs and resistance of the case.

Vaccine therapy (see also article on BACTERIAL VACCINES, this volume) has likewise been praised, but the number of cases reported in which it has been tried has been too few to warrant an opinion as to its actual value.

Autogenous vaccines prepared from the sputa yielded good results in 3 cases of acute bronchitis, 1 of chronic bronchitis, and 4 of chronic bronchitis associated with attacks of spasmodic asthma. R. H. Babcock (N. Y. Med. Jour., Jan. 8, 1916).

The writer uses **stock vaccines** of the Van Cott formula. The first dose given is a large one, to excite the formation of a great amount of antibodies. The interval between doses is always at least 4 days, and is lengthened to a week or 10 days as improvement takes place. **Codeine**, $\frac{1}{4}$ grain (0.016 Gm.) every 2 hours, is often given to procure temporary relief before the action of the vaccine is brought into play. A typical dose of vaccine contains 50 million streptococci, 100 million each of colon bacilli and pneumococci, and 500 million staphylococci. The improvement following each dose depends upon the severity of the reaction, which is partly local and partly systemic. Great care is taken to eliminate cases of tuberculous infection. H. A. Cables (Lancet-Clinic, July 22, 1916).

The writer has had no failures in many cases of chronic bronchitis treated with an **autogenous vaccine** injected at 3-day intervals, in the doses of 1, 2 and 3 c.c. There was no further coughing after this, and no expectoration by the third injection, in a case in which 600 Gm. were expectorated daily, also in 1 in which there was a gangrenous process in the left lower lobe and adhesions preventing pneumothorax. In the latter, 14 injections of the autogenous vaccine were required before the cure was complete. G. Stradiotti (Rivista Critica di Clinica Med., Aug., 1920).

[In true *asthenic* cases, even when emphysema is present, **strychnine** is quite

effective when given in $\frac{1}{40}$ -grain (0.0016 Gm.) doses after meals. As it stimulates the vasculocardiac tone, more blood is driven through the lungs and oxidation is improved, while the nutrition of the body at large, and of the bronchial mucosa in particular, is correspondingly favored. Inhalations of pure oxygen and an out-of-door life aid materially the curative process. The "expectorants," apomorphine, tartar emetic, ipecac, etc., and opiates are more hurtful than beneficial. An important feature of these cases is the preservation of the blood's alkalinity; ammonium carbonate and the measures indicated for this purpose are indicated in the catarrhal form.

Both in senile and in gouty cases, potassium iodide in 5-grain (0.3 Gm.) doses in a glassful of water immediately after meals, very gradually increased until 10 grains (0.65 Gm.) are taken three times a day, often procures striking results.

Small doses (1 grain—0.065 Gm.) of thyroid gland, taken also three times a day, are more active in some cases. Digitalin is another valuable remedy in such cases, but in larger doses than those generally prescribed, especially when cardiac dilatation is present. Beginning with $\frac{1}{10}$ grain (0.0064 Gm.) after meals, it should be very slowly increased until $\frac{1}{4}$ grain (0.0162 Gm.) is taken, carefully watching the case; if the patient complains of a feeling of constriction about the chest, the dose should be reduced. When the pulse is flabby and the skin hypothermic, the patient being very sensitive to cold, quinine hydrochlorate in 3-grain (0.2 Gm.) doses after meals is useful, especially when given with potassium iodide, without, however, exceeding the 5-grain (0.3 Gm.) doses of the latter. Ed.]

Mild cases of broncho-oidosis of the tropics, according to Castellani, and those of medium gravity respond quickly to potassium iodide, 10 to 20 grains, three times daily. When this salt causes severe iodism, salodine in the same dosage, in cachets, may be given. The balsamics and tonics are also useful. The diet should be nourishing.

B. R. Rachford (Arch. of Pediat., July, 1914) found that recurrent rhinitis and recurrent sibilant bronchitis, which are

sometimes associated with rather severe asthmatic attacks and almost always with a severe paroxysmal cough, are very commonly caused by some kind of food intoxication. They may be in most instances almost or quite relieved by dietetic treatment. This symptom group occurs not infrequently in children who have a predisposition to migraine, recurrent vomiting, and urticaria. In the adult and older child, the author uses the following formula:—

R. Sodii sulphatis

(dry) gr. xxx (2 Gm.).

Sodii salicylatis ... gr. x (0.65 Gm.).

Magnesii sulphatis. gr. L (3.3 Gm.).

Lithii benzoatis ... gr. v (0.3 Gm.).

Tinct. nucis vom-

ica gtt. iij.

Aqua destillata .. f3iv (120 c.c.).

The solution is put up in siphons and charged with carbonic acid, and the patient is directed to take, $\frac{1}{2}$ hour before breakfast, a sufficient quantity to produce at least one bowel movement during the morning. This prescription is of great value in the preventive treatment of migraine.

BRONCHIECTASIS.

Bronchiectasis, or dilatation of a bronchus or bronchiole, is always secondary to chronic disease of the bronchi and lungs. Chronic bronchitis is its most common cause; peribronchitis, pulmonary sclerosis or chronic pneumonia, tuberculosis, pleurisy, and emphysema are other conditions in which it often arises.

SYMPTOMS.—The symptoms of bronchiectasis are those of a cavity or of cavities superimposed on those of one of the diseases which are complicated by it. Small cavities cannot be detected by physical examination. The secretions in them are often expelled periodically by coughing. This is especially apt to be the case if a cavity is large and the secretion is thin or serous. Sometimes a cavity can be best emptied by lying upon one side or in a particu-

lar position, because it is best drained in this way. Cavities, when empty and large, produce areas of resonance, and over them the respiratory sounds are bronchial or cavernous. More frequently over them bubbling râles are heard constantly or often. If a cavity is filled with fluid or nearly so it will produce an area of dullness, over which coarse, moist râles will be heard. Frequently these latter signs will be detectable when a patient first awakes, and will gradually disappear and be replaced by those of an empty cavity when coughing has lasted long enough to clear it of what has accumulated during sleep. In tuberculosis it is rarely possible to determine by clinical examination whether we have to do with a tubercular cavity or bronchiectasis. Elastic fibers in the sputa, especially such as exhibit the shape or contour of alveoli, are not uncommon when it comes from tubercular cavities, and equally rare when there is bronchiectasis. However, they may be seen when ulceration takes place in either.

In children mild forms of bronchiectasis may exist which seldom cause symptoms; weeks and months may pass before any functional disturbances can be observed. The bronchiectasis thus escapes detection until some casual infection of the air passages above extends to the dilated bronchial tubes. General symptoms then rapidly develop, sometimes serious, with peribronchial and pulmonary disturbances and signs as of cavity formations. These local phenomena may prove misleading, but, correctly interpreted, they clear up the diagnosis. The fever is often high, with a wide range, the pulse rapid, and there may be a distressing cough, especially when the temperature runs up. The sputum is purulent, but not fetid as in adults, and the dyspnea is generally moderate. The chest may be retracted on one side

and the wall less movable, with impaired resonance or actual dullness over the lesion. In the intervals between the exacerbations of the catarrh the râles may subside, but the cough arouses them again. The younger the child, the greater the chance of recovery; but every catarrhal affection retards this and increases the tendency to sclerosis of the lungs. Such children should be guarded carefully and particularly shielded from contact with tuberculosis. Differentiation from established tuberculosis is often difficult, but the overrapid development of signs of a cavity, their location at the base of the lung, and absence of tubercle bacilli in the sputum, together with the antecedents, should suggest bronchiectasis. V. Hurlin (*Jour. Amer. Med. Assoc.*, from *Presse médicale*, Feb. 18, 1911).

If well drained a bronchial dilatation may remain open and undergo little change for years. If obstructed it may be converted into a cyst, and later its liquid contents absorbed and solid contents converted into cheesy or calcareous matter. Bronchiectases sometimes contract, especially when they are thus obliterated, or when increased air-pressure in them ceases, because coughing is less frequent and severe or has disappeared, or when secretions cease to distend them. Although subject to these changes, a dilated bronchus never becomes normal.

PATHOLOGY. — Dilatations of one or more bronchi or bronchioles occur most frequently in the medium-sized tubes, and least in the largest. They may be numerous, and in both lungs in the same case. They are seen more frequently in the lower and middle lobes than in the upper. Usually only one dilatation occurs in a bronchus, but many may occur in a chain, each generally separated from the other by a narrowing of the bron-

chus. They may be fusiform, round, or angular. Oftentimes the bronchus beyond the cavity is obliterated and the lung-tissue to which it leads collapsed and destroyed. The mucous membrane lining them may be unusually smooth or rough. The cavities which dilated bronchi form differ from others by having bronchial tissue in their wall, by having a single bronchus enter them, and by not being traversed by bands of connective tissue or blood-vessels. They are often ulcerated. The normal tissue is frequently in part, and sometimes even mostly, obscured or destroyed by inflammatory exudates and granulation tissue.

The writer observed 6 cases in which all the symptoms of bronchiectasis were due to the presence of foreign bodies in the lung. These were opaque to the Röntgen ray, otherwise they would not have been discovered. He uses radiography in every case and, because of the possibility of some foreign bodies not showing in a radiograph, bronchoscopy also. Chevalier Jackson (*N. Y. Med. Jour.*, Nov. 6, 1915).

Five cases with autopsies showed that when symptoms and signs point to advanced pulmonary tuberculosis, and sputum examinations do not show the tubercle bacilli, the condition is not tuberculosis. They also showed the disproportion between the signs in the lungs and the constitutional symptoms. McCrae and Funk (*Trans. Amer. Med. Assoc.; Med. Rec.*, July 1, 1916).

The post-operative bronchiectasis following tonsillectomy and the removal of anedoids under general anesthesia, especially in adults, is emphasized, 8 cases having been observed within a few months, while 25 per cent. of all lung suppurations coming to the Radiographic Department of Mt. Sinai Hospital had followed operations of this character. As an aid to the customary history and physical examination, the X-ray

and the bronchoscope have proven of very great value. H. Lilienthal (*Annals of Surg.*, July, 1916).

During the last 29 years, 29,700 patients were admitted to the Brompton Hospital; of these, 567, or 1.9 per cent., were cases of bronchiectasis, 59 per cent. being males, and 41 per cent. females. Among 108 cases examined after death, the bronchiectasis was bilateral in 47, unilateral in 61. In 18 cases all 5 lobes of the 2 lungs were bronchiectatic. Amyloid disease was recorded in 6 of 108 post mortems. Bronchiectasis is always secondary to some other condition; in this series the primary conditions were: chronic bronchitis 41, pleurisy with pneumonia 27, bronchial obstruction from various causes, new growth, foreign body, aortic aneurysm and syphilitic stenosis 37 cases. The most interesting complication of the bronchiectasis noted in this series was intracranial abscess in 15 of the 108 fatal cases. A. J. Jex-Blake (*Brit. Med. Jour.*, May 1, 1920).

Dilatation of bronchial tubes is caused sometimes by ulceration or inflammation, which weakens the wall of the tubes. Coughing produces increased air-pressure within them and gradually stretches them. Ulceration often increases their size and makes them irregular. At other times peribronchitis and chronic pneumonia produce scar-tissue about bronchi, which gradually contracts and tends to stretch their walls. The increased pressure of air in them caused by coughing also helps to dilate them. Cavities formed in this way are usually fusiform and small. However, if pleurisy has fixed a lung to the thorax and bands of new-formed tissue extend through it from such firm attachments, the bronchi in it may be stretched considerably.

In chronic bronchiectasis it is a probable assumption that some of the smaller bronchi are left permanently

diseased and enlarged; this is particularly liable when influenza bacilli are involved. The tendency to the chronic affection is more marked the younger the children. In 18 of 20 children with recurring bronchopneumonia the first attack occurred before the age of 6, in 9 before the children were 2 years old. The acute onset and apparently complete subsidence speak against a tuberculous nature of the trouble. Vogt (*Jahrbuch f. Kinderheilkunde*, Dec., 1911).

Pulmonary gangrene occurs occasionally as a complication of bronchiectasis, when the putrid contents of a cavity invades neighboring tissues after causing ulceration of the bronchial wall. The expectoration is usually profuse and characteristically offensive, and when collected in a vessel separates into three layers, the upper of which is thick and frothy, the middle thin, brownish or greenish, and the lower a dirty green-brown sediment containing gangrenous lung tissue. Unlike the typical pulmonary gangrene, however, that of bronchiectasis is sometimes temporary, the normal symptoms of the chronic bronchitis and its less alarming complications resuming their ascendancy when the gangrenous material has been eliminated. EDITORS.

TREATMENT.—Treatment is chiefly that of the primary disease. Dilatations are kept small and prevented from forming by preventing coughing or by making it light, and by preventing the formation of copious exudates in them, and by lessening or preventing ulceration.

Rest, housing, climatic change, expectorants, and anodynes may meet the first indication. A residence in dry, clean air and the administration of **turpentine** and **volatile antiseptics** may meet the second. These latter remedies and the inhalations of volatile antiseptics will help the last.

In the treatment the pulmonary condition must be considered as well

as complications and the improvement of the general health. The **postural method** is of use in emptying the cavity. Where the latter is near the base of the lung, leaning over the side of a couch or bed with the hands resting on the floor may bring away some of the secretion. **Emetics**, preferably wine of **ipecac**, may also be employed for the same purpose. For the fetor the inhalation of substances which excite cough or expectoration are alone of any service. **Eucalyptol**, **thymol**, or **oil of pine** may be placed in a jug half filled with hot water which is closed by an inhaler. One of the many forms of dry inhalation may be used, the patient drawing the air through a sponge saturated with **tar**, **creosote**, **carbolic acid**, **terebene**, or **iodine**. Any of these may do good in mild cases, but their action is neither so continuous nor penetrating as the **creosote-vapor bath**. Where this method is employed a small room must be set apart for carrying out the treatment; it must be rendered as nearly air-tight as possible. The patient is placed in the room, having previously stopped the nostrils with cotton-wool and protected the eyes with loose-fitting goggles or with watch-glasses fastened over the eyes with sticking plaster. These precautions are necessary, as the vapor is irritating to mucous surfaces. About 3 ounces of liquid coal-tar creosote is placed in a metal dish, which is heated by a spirit lamp. The vapor permeates the whole of the small room. At first it is sufficient for the patient to remain in the room about ten minutes and on alternating days. Subsequently, however, the duration is increased to one hour every day, and the treatment should be continued for a period of two months. The patient, as a rule, feels so much benefited by this treatment that he soon forgets the unpleasant effects of the vapor, such as violent coughing.

Another method is by **intratracheal injections** composed of 1 dram (4

Gm.) of the following solution: **Menthol**, 10 parts; **guaiacol**, 2 parts; olive oil, 88 parts; the injection to be used twice daily. The internal administration of antiseptic and deodorizing agents has long been employed; such substances as **terebene**, **tar**, **creosote**, **copaiba**, **thymol**, **eucalyptol**, and **guaiacol** are best administered in capsules. The best results have been secured by the use of oil of **garlic** in a dose of $\frac{1}{2}$ minim (0.3 c.c.) three times a day.

Mechanical treatment is useful in addition to the postural method which has already been described. This consists of expiratory compression of the chest and abdomen. S. Box (Practitioner, June, 1906).

Tannin and **calcium biphosphate** exercise a marked vasoconstrictor action upon the pulmonary tissues; they also modify and deodorize the purulent expectoration. The writer administers 4 powders daily, each containing 4 grains (0.25 Gm.) of each drug. If hemoptysis occurs the quantity of the tannin may be increased by one-half. During the treatment the patient should drink only water, for all other liquids, especially alcohol, are contraindicated. Marini (Jour. des praticiens, vol. xiv, p. 219, 1907).

The medical treatment is largely palliative. The adoption of a semi-erect posture facilitates drainage of the apical cases. After **intratracheal inflations** the patient should be placed in the recumbent position. Autogenous **vaccines** might be tried, although their value was undetermined. McCrae and Funk (Trans. Amer. Med. Assoc.; Med. Rec., July 1, 1916).

Case in which the bronchiectasis was of several months' standing, the cough distressing, and the sputum extremely malodorous, but no tubercle bacilli were found. One lung seemed normal but the temperature kept subfebrile. The man was growing weaker, and there seemed no hope from an operation. The writer then resorted to **raising the foot of the bed** by 40 cm., and gave him

potassium iodide freely. At first this slanting position was maintained only one hour in each four, but the benefit was so prompt and so marked that the man begged to have the bed kept slanting all the time. The expectoration diminished, the cough subsided and in 7 weeks the man left for his farm completely restored. One young girl given similar treatment was found in robust health a few years later. The iodide and copious drinking diluted the sputum and the sloping position ensured its expulsion. De Jong (Neder. Tijdsch. v. Geneesk., Feb. 16, 1918).

Endobronchial treatment of bronchiectasis and bronchial abscess recommended. The apparatus employed was devised by Yankauer, and consists of a double tube, the outer one to be attached to the suction apparatus and the inner one to the irrigating apparatus. **Morphine** and **atropine** were given half an hour before treatment, followed by thorough **cocainization** of the mouth, tongue, pharynx and larynx. The patient lies on his back with his head supported by a trained assistant, the bronchoscopic tube is inserted, and a spray of 2 per cent. **cocaine** and **adrenalin** is thrown into the bronchus to allay coughing. The excessive secretion in the bronchi is then withdrawn through the tube by the suction apparatus, and 10 ounces of **warm salt water** slowly introduced through the inner tube are at once withdrawn through the outer one. The patient later receives a solution of **iodine**, 2 drams (8 Gm.) and **phenol**, 15 mm. (0.9 c.c.), to 1 pint (500 c.c.) of water. This method was repeated weekly in each case, with no serious results. There was almost complete cessation of odor, especially after the use of iodine, and a diminution in the amount secreted—at least, expectoration was very much easier. Decided improvement was also noted in the general physical condition of the patient. Emil Mayer (N. Y. Med. Jour., Oct. 19, 1918).

Bronchiectasis necessarily increases the discomfort of those having chronic pulmonary diseases, and may lead to fatal results when ulceration is extensive in them or, as sometimes happens, they are the focus from which gangrene of the lungs springs. Suppuration in them may produce a hectic fever, slow wasting, and ultimate death.

Surgical measures have recently been recommended, and have given good results in suitable cases.

Treatment of 26 cases showed that a single focus, or multiple foci in 1 lobe, can be removed surgically. Even when an abscess has extended so as to implicate neighboring lobes in one single infected mass, extirpation may be performed successfully. Lilienthal (Annals of Surg., July, 1916).

The writer operated on 4 patients who had been given systematic internal treatment for more than a year in vain. All were greatly benefited or clinically cured by the **subperiosteal resection** of from 13 to 20 cm. of 4 or 5 ribs, suturing in 2 tiers with a compressing pad above. One patient was thus completely cured in 5 weeks from a year's disturbances from profusely secreting fetid bronchiectasis. There was some persisting pain in the region for a time, but this gradually wore off. He advises subperiosteal resection first, and only if this proves inadequate, removal of the periosteum and intercostal muscles, with internal measures as required. J. H. Zaaijer (Neder. Tijdsch. v. Geneeskunde, Feb. 19, 1916).

In 5 complete **resections of the lower lobe of the lung**, with 1 death, the writer concludes as follows: 1. Advanced bronchiectasis cannot be cured by medications, inhalations, intratracheal injections, intratracheal irrigations, climatotherapy or vaccines. 2. Collapse therapy produced either by nitrogen, artificial pneumothorax or by surgical measures is not curative. 3. Pulmonary arterial ligation is of more definite value as a preparation for lobectomy than as a

curative measure *per se*. 4. Excision of the diseased portion of 1 lung is the only curative treatment of advanced bronchiectasis. Robinson (Surg., Gynec. and Obstet., Feb., 1917).

Simple pneumotomy, as well as extrapleural thoracoplasty, proved disappointing in bronchiectasis in the writer's experience. In 4 other cases he removed the diseased part of the lung. One patient died from pleuropneumonia in the other lung but the other 3 made as complete a recovery as could be expected. While **thoracoplasty** alone is of little service, it is quite rational to do more or less extensive plastic work on the chest wall, besides excising the diseased lung tissue. P. N. Hansen (Nord. med. Ark., i, Kirurgi, No. 13, 1917).

N. S. DAVIS, JR.,
Chicago.

BRONCHITIS, CAPILLARY.

See BRONCHOPNEUMONIA.

BRONCHITIS, FIBRINOUS, PLASTIC, OR MEMBRANOUS.—

This is a form of bronchitis which may be acute, subacute, or chronic, but it belongs, as a rule, to the latter group, in the sense that the attacks are generally repeated at intervals, weeks, months, or even years. It is an inflammation of the mucosa of the larger and medium tubes, attended by the formation of an exudate or false membrane which tends to form casts of the bronchial tree.

SYMPTOMS.—The general symptomatology of fibrinous bronchitis is relatively scant, the phenomena, prior to the expulsion of the false membrane, being scarcely distinguishable from those of the ordinary type of catarrhal bronchitis. Violent paroxysms of cough, with at times marked dyspnea and even cyanosis and scanty expectoration, tend to suggest its existence, but any doubt that may exist is soon removed by the expulsion of

casts or patches. The paroxysm is usually preceded and followed by the catarrhal phenomena of bronchitis, but after the detachment of fibrinous false membrane from the bronchial mucosa a more or less profuse mucopurulent expectoration appears. The paroxysm is sometimes attended by hemoptysis, which may assume the importance of a serious hemorrhage, but this ceases, as a rule, as soon as the fibrinous cast is removed. But little suffering is usually complained of, other than the discomfort attending the racking cough and the diaphragmatic pain which sometimes accompanies it. The temperature may rise to 104° F. (40° C.) in acute cases and in the course of exacerbations. Rigors, more or less severe and prolonged, are sometimes witnessed, and the picture at the outset may suggest pneumonia.

The physical signs, at least those elicited by percussion and auscultation, are practically those observed in chronic catarrhal bronchitis, the difference being that what signs are clearly defined are less diffuse, *i.e.*, especially marked in circumscribed areas, probably where the false membrane is partially detached, as to auscultation, and where the membrane is thickest, as to percussion.

An attack of fibrinous bronchitis may subside after a few days, but the disease may persist many years, with occasional acute exacerbations. The outlook is more favorable in adults than in children, unless it is associated with other affections: pulmonary tuberculosis or fibrosis, pneumonia, or emphysema. In infants and young children the mechanical obstruction of the bronchi sometimes produces fatal asphyxia.

ETIOLOGY AND PATHOLOGY.—The former habit of ascribing to syphilis or tuberculosis practically any respiratory disease when its pathogenesis was unknown caused fibrinous bronchitis to be connected with these diseases etiologically, but they are now known to occur together concomitantly, *i.e.*, as a coincidence. The infections referred to tend greatly to aggravate an existing fibrinous bronchitis or even facilitate its development in predisposed subjects, however, the disease being often a familial one in the sense that several members of a family may suffer from it. It is, moreover, often associated with tuberculosis and occasionally with asthma, emphysema, membranous laryngitis, pneumonia, typhoid fever, disorders of menstruation, and certain cutaneous disorders. An attack of acute bronchitis due to exposure may initiate it.

Fibrinous bronchitis usually starts pathologically with hyperemia of the bronchial mucosa, soon followed by swelling and infiltration, sometimes amounting to actual edema. Gradually the mucosa becomes covered with a grayish or pearl-colored adherent and tenacious exudate, which thickens and develops into the false membrane. The latter is mainly composed of fibrin and lymph, leucocytes, fat-droplets, and epithelial cells. Curshmann's spirals and Charcot-Leyden crystals are also found in most cases. The casts may, on being immersed in water, be unrolled with needles; if placed in a solution of acetic acid they become greatly swollen, while ordinary mucus contracts.

TREATMENT.—While the treatment does not differ in its general lines from that of other bronchitis, an

essential feature must be borne in mind, viz., the probability that the formation of false membrane is due to imperfect osmosis of the body fluids. Hence the value of alkaline salts, especially the **sodium carbonate** (not bicarbonate), 5 to 10 grains (0.3 or 0.6 Gm.) every three hours in a glassful of water, and colonic injections of **saline solution**, at least 1 pint daily, retained as long as possible, after cleansing out the rectum. The casts being soluble in **lime water**, a spray of this agent, the patient breathing deeply, has been found useful. **Ammonium chloride** facilitates the elimination of the false membrane by increasing the activity of the bronchial acini and also the fluidity of the secretions.

In chronic and recurrent cases **ichthyol** used as recommended under chronic bronchitis (*q.v.*) has been found very helpful. **Potassium iodide** is also of great value.

The use of opiates or of any agent calculated to stay the cough is pernicious, since it contributes to the retention of the false membranes, thus aggravating the case and increasing the danger of suffocation through the obstruction to the respiratory function their accumulation entails.

C. E. DE M. SAJOURS,
Philadelphia.

BRONCHOPNEUMONIA.—

SYNONYMS.—Lobular pneumonia, catarrhal pneumonia, bronchovesicular pneumonia, disseminated pneumonia, bronchoalveolitis, bronchoalveolar catarrh, peribronchitis (Bälzer), capillary bronchitis, suffocative catarrh.

DEFINITION.—An inflammation of the terminal bronchus and the air-

vesicles which make up a pulmonary lobule, usually affecting many comparatively small areas of contiguous and neighboring lobules in both lungs and in all lobes.

VARIETIES.—There are recognized two principal types of the disease: the *lobular*, in which the dissemination of the morbid process and the distinctly lobular involvement of the alveoli can be readily demonstrated, and the *pseudolobar*, in which the massing and extent of the affected areas give a resemblance to the consolidation of croupous or lobar pneumonia. To these may be added that type which was, at one time, clinically distinguished as *capillary bronchitis*. Cases may also be separated according to their *origin* and *mode of onset*. Those which are the first and independent result of infection or injury are termed *primary*. They are less common than the *secondary cases*, which supervene upon acute or chronic infectious maladies, especially whooping-cough, the exanthemata, and tuberculosis, or which complicate widespread infections of various kinds. Both primary and secondary cases may develop *frankly* or *insidiously*. Also *terminal infection* in Bright's disease, diabetes, etc., and even in simple asthenia of old age may take the form of catarrhal pneumonia.

SYMPTOMS.—As the severity of the pathological processes varies greatly in different cases, the symptoms have corresponding variability. Necessarily, too, the primary and secondary cases differ in onset and development. In some primary cases the general symptoms are so slight that the patient walks around attending to his usual affairs, or, if a child, plays

about, with but slight complaint except of cough, or, as is likely to be said, of "cold." This is not infrequent at the beginning of an attack of influenza, which may afterward prove quite severe, if unattended to; and it is the rule in the early stages of tuberculosis. The mistake of looking upon the case as one of simple bronchitis may thus easily be made.

Elevation of temperature, often surprisingly great, will, however, be discovered upon thermometrical examination; percussion and auscultation of the chest will reveal some of the characteristic physical signs. There may be slight pain in the chest, especially if there be pleural involvement, and this is more common in influenza and tuberculosis than in other varieties of the affection. In other cases the symptoms, though rarely, except in influenza, sudden in onset, become quite severe from the first; there is prostration, with high fever, rapid pulse, headache, restlessness, pain in the chest, and respiratory distress, with quickened breathing, cough, and usually expectoration; though in children in whom the morbid process ensues as a sequela of some infectious fever the cough is at first dry and harsh. In infants and young children, moreover, there is often difficulty or even impossibility of expectoration, so that the moist sounds of air passing through the mucus retained in the windpipe and bronchi may be audible even to the casual observer, and there is then considerable distress in respiration, often approaching suffocation, thus giving rise to the common synonym of capillary bronchitis: suffocative catarrh. The matter expectorated is not, as a rule, blood-stained, but varies much in its physical characteristics. It is usually mucoid; sometimes, and especially

in tuberculosis, mucopurulent; and in influenza often resembles boiled sago sprinkled with coal-dust. I have come to look upon this black discoloration of the influenzal sputum as quite characteristic. Whether it is common, outside of dusty cities, I do not know. The appetite is impaired, the tongue coated, the lips red and dry at first, afterward cyanotic. The skin is dry and hot. In cases beginning insidiously, the symptoms may suddenly develop after a previous unmarked stage of general depression, or the distress may be of gradually increasing severity.

Both sudden and gradual onset of bronchopneumonia is observed during the progress of the exanthemata or whooping-cough. Although in measles catarrhal symptoms mark the onset of the malady, they may clear up, and bronchopneumonia be manifest only when convalescence should be declared.

Out of 56 cases studied by Nicoll, vomiting occurred 6 times, convulsions in 5; chills were noted in 2 cases, and looseness of the bowels was frequent. The writer believes that the most noticeable remittency in temperature is seen in the cases in which the influence of the streptococcus predominates. A critical ending occurred only 9 times in 167 cases. The diagnosis between bronchopneumonia and meningitis is often difficult, for, in both, spasm of groups of muscles, tache cérébrale, Kernig's sign, and rigidity of the neck may occur.

Case in which Brudzinsky's sign, heretofore observed only in diseases of the nervous system, such as meningitis, etc., was observed. It is elicited by forcibly flexing the head with one hand while the child is lying flat on his back and using pressure with the other hand on the chest to prevent its being lifted. If the sign is positive both legs will flex on the thighs and the thighs on the abdomen. M.

J. Loeb (Jour. Amer. Med. Assoc., May 13, 1911).

The *Streptococcus hemolyticus* is capable of causing fatal epidemics of interstitial bronchopneumonia. The condition arises with or without such predisposing causes as measles, but seems especially severe after that disease. There is often also a diffuse, patchy, lobular pneumonia in which the streptococcus is finely scattered in the alveolar exudate. Such areas may be confluent and resemble lobar pneumonia. Ulceration of the vocal cords and epiglottitis and empyema are frequent complications. MacCallum (Jour. Amer. Med. Assoc., Aug 31, 1918).

Physical examination at first, especially in children, may fail to reveal dullness or even blowing breathing, but there will be discovered, scattered over both lungs and often more frequent and more extensive at the bases, showers of fine, subcrepitant râles. Sibilant rhonchi may likewise be heard. In the course of a day or two, sometimes later, scattered areas of dullness associated with bronchial or vesiculobronchial breathing, and moist râles, and sometimes with absence of breath-sounds, indicating atelectasis, are discovered. Of these some are constant and others appear and disappear: shifting dullness. They are found upon both sides, and may be numerous and small, or few and extensive. Sometimes they are massive, involving the greater portion of a lobe or of a lung. These massive areas are constant, and over them the breathing is distinctly bronchial, closely resembling that of lobar pneumonia. Bronchophony may be present. In tuberculosis, what I have termed "the isolated apex sibilant râle" is quite characteristic. An apex pleuritic friction is sometimes heard, and usually as the case progresses there develop characteristic crackling, and the liquid râles indicative of softening.

As these signs develop, indicating extension of the local morbid processes, the symptoms become correspondingly severe. Dyspnea increases and the respiration rate rises, with children reaching 60 or 70, with adults rarely exceeding 50, and usually remaining below that number. Cyanosis now becomes manifest. There may be supra-sternal and infrasternal retraction. At first, in severe cases, the children exhibit great restlessness and anxiety, but, as asphyxiation progresses, sensation becomes obtunded, drowsiness increases, and, while the breath becomes more gasping, the efforts to obtain air diminish. The heart becomes weaker; the right ventricle is evidently distended; the pulse is small, feeble, and fluttering, and death may occur from cardiac paralysis or from exhaustion. Sometimes there is delirium, cephalalgia, retraction of the head, and tenderness of the scalp and neck, apparently indicating meningeal complications, and convulsions may occur; at other times there is constant or intermittent delirium, with jactitation, and this seems to be rather toxemic than due to cerebral inflammation.

Recovery may take place even in apparently desperate cases, and the symptomatic changes may be as sudden as in lobar pneumonia, though usually the process is gradual, but rapid. The duration varies from about ten days to about three weeks. In cases delayed beyond this the suspicion of tuberculosis or localized empyema becomes strong. Some cases, however, which are not clearly tuberculous, run a remittent or subacute course, and others gradually take on a chronic type.

DIAGNOSIS.—It is the frank primary cases and those of insidious onset that cause difficulty in diag-

nosis. Cases clearly secondary ^{to} whooping-cough, the exanthemata, etc., usually tell their own story.

There used to be much written concerning the differential diagnosis of capillary bronchitis and bronchopneumonia. Post-mortem investigation has shown that the differentiation is impossible, for the two conditions usually coexist. The difference is symptomatic only, and affects treatment only as this is guided by symptoms.

It is a question whether in children all cases of apparent acute bronchitis should not be considered, at least potentially, as bronchopneumonia. Similar caution as to the aged is also desirable. A tendency to recurrence is always suspicious. Apart from this the physical signs of consolidation differentiate, and in simple bronchitis, moreover, the marked depression is absent.

Typhoid fever sometimes begins with signs of bronchopneumonia. Caution and careful observation will usually direct attention to the true state of the case. As it progresses the characteristic temperature, the splenic enlargement, the rose spots, clear up the diagnosis.

Apart from the recognition of influenza as the basic condition—a fact frequently overlooked when epidemics are not manifest—the chief difficulties are to determine whether or not lobar pneumonia exists in a case presenting massive areas of dullness, and to determine whether or not a case of recognized bronchopneumonia is tuberculous.

Lobar Pneumonia.—As to lobar pneumonia, it is to be remembered that this is less frequent, though not altogether rare, in the aged and in chil-

dren under 5 years of age. Between 5 and 60 there is little diagnostic dependence to be placed on age. The mode of onset is usually different, lobar pneumonia developing abruptly with chill, lobular pneumonia coming insidiously and, as a rule, being a secondary infection. Lobar pneumonia is usually one-sided and limited; bronchopneumonia is usually scattered over both lungs. Even when lobular foci are massed, it is more common to find the other side involved than in lobar pneumonia. Yet there are cases, severe and often fatal, of lobar pneumonia beginning insidiously and extending from one region of the lung to another and from one side to the other, or even bilateral from the beginning; so that these points of distinction are far from absolute. The physical signs are of greater certainty. In lobar pneumonia the physical signs of consolidation are persistent until resolution begins. Some shifting dullness is usually found in bronchopneumonia. The râles of lobular pneumonia are rather subcrepitant than crepitant, and the ringing râle is much more frequent than in lobar pneumonia. Rusty sputum is the rule in lobar pneumonia, the exception in lobular pneumonia. Pneumococci may be present in pure culture and, at least, commonly predominate in lobar pneumonia; other organisms are frequent in bronchopneumonia. Yet, this is by no means an infallible test. A high leucocytic count is usually in favor of lobar pneumonia; but a low count does not imply its absence. Lobar pneumonia most frequently terminates by crisis from the fifth to ninth day; bronchopneumonia is more prolonged and subsides by lysis.

A well-marked leucocytosis is present in the bronchopneumonia of chil-

dren, and is independent of the amount of lung involved. The degree of leucocytosis in bronchopneumonia stands in no relation to the height of the temperature. Though there are some exceptions, yet in bronchopneumonia the general rule is that failure of the leucocyte count to drop when the pulmonary signs disappear indicates either a complication or a fatal termination of the illness.

A constant and considerable leucocytosis may regularly be expected in the lobar pneumonia of children. The degree of leucocytosis is about the same as in bronchopneumonia (bronchopneumonia: average leucocytosis in 19 cases, 33,900; lobar pneumonia: average leucocytosis in 24 cases, 31,700). The leucocytosis in lobar pneumonia differs from that in bronchopneumonia in that the white blood count is higher when the pulmonary involvement is greater. If in lobar pneumonia two or more lobes be involved, a relatively high blood-count may be looked for. The leucocytosis in lobar pneumonia furnishes no clue as to the height of the temperature. An increasing leucocytosis is the general rule in the lobar pneumonia of children, reaching the maximum just before the crisis. While failure to drop before the crisis may indicate a complication, yet this may be of special significance. The pre-critical drop in the lobar pneumonia of children is inconstant, of little or no prognostic value, and cannot be utilized as means of determining the time of crisis.

There is a high leucocytosis at the onset of empyema in children. In general, it may be said that the diagnostic value of the leucocytosis in the pulmonary affections of children is limited. In certain instances, however, the leucocyte count is of great diagnostic aid. When, for example, in lobar pneumonia, resolution and the drop in the leucocytosis have occurred, and there are present signs exciting suspicion that empyema will be a sequela, then blood-counts should frequently be made at regular

intervals. A sharp rise in the count, provided that other causes of leucocytosis can be excluded, is then strong presumptive evidence of a supervening empyema. Henry Heiman (Archives of Pediatrics, Oct., 1905).

In the first count made by the writer in a case of bronchopneumonia, the leucocytes numbered 130,000 per c.mm. Seven hours later they were 144,000 per c.mm.; on the following morning they had increased to 183,000 per c.mm., and on the same evening reached a maximum of 206,000 per c.mm. During the following four days the leucocytes varied between 126,000 and 156,000, but with the onset of a mastoiditis again rose to 192,000 per c.mm. Austrian (Johns Hopkins Hosp. Bull., Aug., 1911).

Tuberculous Bronchopneumonia.—

This form is much more common both in adults and in children than was formerly supposed. Many cases of so-called bronchitis in infants and children are of tuberculous origin, perhaps extending from the glands. At Jefferson Medical College Hospital, where I saw many children and adolescents in the years 1884 to 1887, I made inquiries as to the antecedents of many of the cases of "cough" of various kinds, and found that there could be separated a group of cases of *recurrent bronchopneumonia* which were almost invariably tuberculous, and probably had been such from the outset. I have also seen many cases of recurrent fever and cough in young people—sometimes without physical signs other than of seeming bronchitis; sometimes, if one times his examination fortunately, with areas of atelectasis—which I am sure are tuberculous and explain the numerous cases of healed and "latent" tuberculosis reported from the dead-house. Indeed, so far from feeling that I am called upon to establish the correctness of the

suspicion of tuberculosis in cases in which this arises I am beginning to feel that the burden of proof rests on the side of exclusion. When a case is far advanced, microscopic examination of the sputum showing lung-fiber or tubercle bacilli clinches the diagnosis. Unfortunately, these signs are not available early and the diagnosis is often exceedingly difficult and doubtful. The points on which more or less reliance may be placed are as follows: 1. The course of the fever, which is usually remittent in simple bronchopneumonia and often hectic or irregular in tuberculosis, though I have seen it sustainedly high and falling by crisis in cases undoubtedly tuberculous. Sometimes the temperature is of the inverse type. 2. The duration of the case, which is more prolonged in tuberculosis, passing into a chronic or subacute course, though death at times occurs early. These cases form the group of *rapid consumption* in young adults, though not rarely recovery or arrest takes place. 3. The antecedents, that is, the personal and family history of the patient. Heredity plays a marked influence; so, too, do causes affecting the health of the parents, even though they themselves do not become tuberculous. Bronchopneumonia following typhoid fever in a young adult is almost invariably tuberculous, and frequently does tuberculosis supervene upon the catarrhal pneumonia of measles and of influenza. 4. The physical signs are likely to be more pronounced in tuberculosis. There is some apical impairment. Crepitant and subcrepitant râles in the middle of a lung are more common. Sibilant râles in isolation are characteristic. As the case proceeds, the signs of breaking down become evi-

dent. The tuberculin test may be applied cautiously, by subcutaneous injection of old tuberculin or of tuberculin residue; or by application of old tuberculin to the skin after the methods of von Pirquet or Moro. The conjunctival method of Calmette is not to be commended in view of the large possibility of accident, but the application may be made to the inner surface of the upper lip, on one side of the frenum. Rosenberger's method of demonstrating tubercle bacilli in the blood and in the feces may prove of value. Positive results obtained by these means of diagnosis are conclusive; I am not prepared as yet to say the same of negative results.

In the early stages of tuberculous bronchopneumonia in infants all the signs are those of an ordinary bronchopneumonia, but these recede, and the only signs of consolidation left are metallic crepitant and subcrepitant râles. Hence a focus of subcrepitant or crepitant râles, localized and fixed, may be considered as evidence of tuberculous bronchopneumonia. Associated with this stage of the disease is a dyspnea without distress or cyanosis; the dyspnea of ordinary bronchopneumonia being urgent and painful, that of tuberculous consolidation leaving the child free from pain, and quite indifferent to the fact that its respirations are double or treble the normal frequency. Associated also with this stage is a rapid wasting, in spite of the absence of fever, vomiting, and diarrhea, and with the presence of a good appetite.

The extrapulmonary signs are the pale, dry, scaly skin; the long eyelashes; the exhausted appearance; the irregular bouts of fever; the enlargement to a very slight degree of the various lymphatic glands; the enlargement of the liver (enlargement of the spleen the writer regards

as uncommon); the extreme susceptibility to cold, and, lastly, the localization of tubercle in the testis, or joints, or bones. G. Mouriquand (Gaz. des hôpitaux, Aug. 1, 1908).

Influenza is usually recognizable by the suddenness of the attack, by the great prostration, by the severe headache, by the cutaneous hyperesthesia and muscular pain, and by the disproportion between the great respiratory distress and the comparative paucity of physical signs. In cases of gradual onset and of extensive pulmonary involvement the diagnosis is much more difficult and depends upon the general association of symptoms. One point in favor of influenza in a given case would be the fact that a comparatively high fever—104° or 105° F.—in an adult is borne with little discomfort, the patient perhaps being scarcely conscious of fever. The character of the sputum, its sago-like appearance, is also significant. The discovery of the characteristic bacilli in the sputum clinches the diagnosis.

The writer recommends the following method of obtaining a pure bacterial culture in bronchopneumonia. He examines the patient's larynx in the usual way with a rather broad mirror, carefully sterilized, and avoiding all contact of the reflecting surface with the mouth. Previous gargling with dilute hydrogen peroxide solution is perhaps advisable. As soon as the larynx is in view, the patient is requested to cough slightly; often he does so spontaneously. Purulent matter is projected against the mirror, which is then withdrawn and supplies material for making cultures on the ordinary media. Where the patient is weak, the procedure can be used while he is recumbent. Rosenthal (Paris méd., Apr. 1, 1916).

The writers observed 9 fatal cases of bronchiolitis and bronchopneumonia, due to *B. influenza* of Pfeiffer, at a base hospital in France, in

1916-1917. Great dyspnea, marked cyanosis, rapid pulse, irregular temperature, the expectoration of large amounts of nummular sputum, and signs of a generalized bronchiolitis (with or without signs of consolidation), were characteristic of the disease. The diagnosis rested ultimately on the finding of Pfeiffer's bacillus as the predominating micro-organism in the sputum. At necropsy this organism was grown in pure culture from the terminal bronchi, and no other organisms were seen here. Two cases showed acute endocarditis due to *B. influenza*, and in one of these the blood culture was also positive for the same organism. These cases apparently were sporadic. Malloch and Rhea (Quarterly Jour. of Med., Jan., 1921).

ETIOLOGY. — Bronchopneumonia is sometimes an independent affection arising from "cold" or from direct irritation by smoke and noxious vapors and gases, and, in cases of such origin, it may likewise be associated with, or arise by extension from, inflammatory processes in the upper air passages. It may be caused by chloroform, and less often by ether, administered for surgical anesthesia in the presence of artificial light by combustion.

It may arise from purely local infection by agents recognized and not recognized, and probably not specific. It may occur in extension from bronchitis of any origin.

It is, however, usually met with as a complication or sequela of one of the infectious diseases, and especially of those of childhood. Even when it is the only or most prominent manifestation of the existence of infection,—as, for example, in influenza or tuberculosis,—it is to be regarded as secondary.

It may be associated with, or follow, measles, scarlet fever, small-pox, whooping-cough, influenza, tuberculo-

sis, erysipelas, dysentery, meningitis, and typhoid fever.

It also occurs from the aspiration of food (schluck-pneumonia, deglutition pneumonia, inspiration pneumonia) or infectious materials in cases of anesthesia or paralysis of the larynx, in coma of any origin, in malignant disease of the larynx and esophagus, following hemoptysis, following operations about the mouth and upper air passages, and in some cases through the inspiration of matters from a vomica or from a bronchiectatic cavity, or, in exceptional instances, from the rupture into the lung of a purulent collection in the pleura, liver, or elsewhere.

Tuberculous bronchopneumonia is the most common and most fatal form. Next in frequency is infectious bronchopneumonia associated with the diseases of childhood, which, according to distinguished pediatric authors, causes more deaths than do the fevers themselves. Rickets and diarrhea are likewise mentioned by authors among the predisposing causes affecting children. Thus, while the disease occurs at all ages, it is much more frequent in childhood and infancy. Old age may likewise be considered a factor in creating susceptibility to the disease, and it occurs in association with the various diseases and degenerative conditions incident to the decline of life. At all ages the disease is most prevalent among the poor.

It is, therefore, essentially a morbid process occurring in persons of lowered or innately poor vital resistance, and in conditions which favor mechanically the entrance of infectious material into the bronchi.

Analysis of 150 fatal cases of bronchopneumonia. All the children were under 13 years of age, and 138 were under 4 years. Sex: 85 of the cases

were in boys, and 65 in girls. Of 64 cases under 4 years of age, 32 were breast fed and 32 were bottle fed. But, estimated on the number of cases that occur, the mortality from bronchopneumonia is 7.7 times as great in bottle-fed as in breast-fed children. Well-marked signs of rickets were present in 16.7 per cent. of all the 150 cases. As regards exciting causes, 15 cases followed measles, 8 meningitis, 5 otitis media, 3 pyemia, 2 administration of anesthetics, and 3 typhoid fever. Both lungs were affected in 132 cases, the right lung alone in 9, and the left alone in 9 also. Confluent or massive bronchopneumonia was present in 6 instances, and suppurative bronchopneumonia in 15. Acute fibrinous pleurisy was present in 15 cases, and serous pleurisy in but 1. Empyema occurred in 16 cases. Hardy (Lancet, Sept. 24, 1904).

BACTERIOLOGY.—Apart from the tubercle bacillus, the organisms most frequently found in bronchopneumonia are *Micrococcus lanceolatus*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *Staphylococcus albus*, *Bacillus pneumoniae* of Friedländer. In cases of diphtheria the Klebs-Löffler bacillus is frequently found, and in influenza Pfeiffer's and other organisms have been reported. It is rare for pure cultures to be found except in the case of the pneumococcus, which is most frequently associated with the pseudolobar type of the disease, the streptococcus being most common in the lobar type. Mixed infection is the rule.

Study of the bacteriological pathogenesis in 53 cases. In 31 of these the diagnosis of the probable etiology was based on examination of the sputum obtained during life, while in 22 cases it was based on the results of post-mortem examinations. The results of the examination of the sputum and of the lungs *post mortem*

permit a division of the case into 4 classes:—

1. Five cases in which cover-glass preparations showed pneumococci only or in very large proportion, both within and without the leucocytes. The appearance in these cases was exactly the same as that seen in cover-glass preparations of the sputum of lobar pneumonia. While other organisms were present in small numbers, the appearance suggested that the lesions were chiefly due to the pneumococcus only.

2. Seven cases in which the influenza bacillus was found in such enormous predominance, both within and without the cells, that the appearance suggested that this bacillus was the chief or only cause of the lesions.

3. Twelve cases in which either the tubercle bacillus was found in the sputum (4 cases), or in which the characteristic lesions of tubercular bronchopneumonia were found at autopsy (8 cases).

4. Twenty-nine cases in which cover-glass preparations suggested a mixed infection. Dunn (Boston Med. and Surg. Jour., May 7, 1908).

From study of sputum and post-mortem material from 3 typical cases of malignant influenzal pneumonia, the writers conclude that while *B. influenza* is the etiologic factor of the primary influenza, the secondary pneumonia and fatal terminations are due to areas of bronchopneumonia caused by *B. mucosus capsulatus* or bacillus of Friedländer. Rucker, Jr., and Wenner (N. Y. Med. Jour., Dec. 21, 1918).

MORBID ANATOMY.—The lungs exhibit inflammatory changes in the bronchial tubes, and areas of pulmonary consolidation, some of which are the result of collapse and some of vesicular inflammation. Collapse is caused by the plugging of the bronchi. The vesicular inflammation arises through hyperemia and edema in obstructed areas; by extension downward from the terminal bronchioles, or, as Balzer has shown, by extension

laterally from the walls of inflamed bronchi.

All the coats of the bronchial tubes are swollen and thickened, and the reddened mucous membrane is usually, but not always, covered with a thick, tenacious, or even puriform mucus. Sometimes the mucus has become inspissated, marking out the course of the bronchi by yellow lines. Fibrinous concretions may be found. On section, especially in children, the cut extremities of the bronchi stand out from the surrounding tissue. Dilatations are observed, which in the larger tubes are commonly fusiform and cylindrical. In the smaller ones they are globular, and the terminal dilatations may attain the size of a milletseed or hempseed. The pleural surface may be studded with such nodules, which yield a yellow fluid when punctured. They may, when distended by inspissated pus, strongly resemble tubercles. Pneumothorax sometimes arises from rupture of these distended globules into the pleural sac.

Atelectasis, especially in children, is largely due to the obstruction of the bronchi by inspissated mucus. In early stages the collapsed area is still distensible by insufflation. This distinguishes it from lung-tissue filled with inflammatory products. Later, the distensibility may be lost. An atelectatic area is generally distinguishable from one of infiltration by being sunk below the level of the surrounding tissue, by its glistening, smooth section, and by the fact that, when the collapse occurs at the surface of the lung, the pleura shows no sign of exudation and still maintains its transparency. Such areas are harder and resist pressure more than inflamed portions of the lung, and when scattered thickly throughout the

organ may give to the finger the sensation of shot-grains.

On scraping or pressure a thick, white fluid escapes, which under the microscope contains proliferated epithelium and leucocytes. Fibrinous exudation is never marked and may be entirely absent from many areas. When vesicular inflammation has occurred in extension from the bronchi the nodules may be microscopic or may reach the size of a hempseed. In early stages they may be dark red, but usually they are of a finely granular, yellowish or dull-white appearance, fading insensibly into the surrounding tissue. If in a collapsed area, however, they stand out rather prominently from a bluish, purplish, or even black background. Abscess or gangrene is sometimes present. Sometimes inflammatory changes may be found scattered through a collapsed and congested part.

Hemorrhagic extravasations are often seen. They are mostly subpleural and petechial, but may be more extensive. Emphysema is almost constantly found; mainly in the upper lobes, especially along their anterior margins. Interlobular emphysema is not uncommon in fatal cases of whooping-cough at early ages.

Resolution is often complete; sometimes dilatation of the bronchi, with some condensation of surrounding pulmonary tissue, persists for a long time, perhaps indefinitely. Chronic induration of the lungs following acute bronchopneumonia is not very rare, if one may judge by clinical observation. In debilitated subjects, especially in children the subjects of scrofula or rickets, caseation and ulceration, not to be distinguished from tuberculosis, supervene. Tubercle bacilli may be found in the neighborhood, but whether of late ap-

pearance, or whether the process has been tuberculous from the first, it is not always easy to determine.

Pleuritis is a frequent complication of bronchopneumonia, but effusion of any extent is not common. Over collapsed portions the pleura is not inflamed, and this may aid in the diagnosis between atelectasis and pneumonia. The bronchial glands are swollen, sometimes distinctly hyperemic. In rare cases they are unaffected. Sometimes they show cheesy spots or calcified nodules, usually in connection with tuberculosis of the lung.

The right side of the heart is usually dilated, and in young infants there may be in consequence persistence of the openings of the foramen ovale and ductus arteriosus. Thrombosis of the pulmonary artery and pericarditis are among the occasional complications.

Other organs show, for the most part, only the results of venous congestion. Edema and congestion of the brain are common in fatal cases. Actual meningitis, however, is rare. Congestion of the liver, the stomach, and intestines is frequent, and erosions may be found in the large intestine. The kidneys are usually congested. Concretions of urates are often found in the straight tubules of the pyramids. Anasarca and ascites are infrequent.

TREATMENT.—While to some extent dependent upon the exciting cause of the pathological process in the individual case, and subject to modification according to age, sex, personal characteristics, environment, and so forth, the general lines of treatment in cases of bronchopneumonia are very much alike in all cases.

In the acute form of the disease rest is necessary, and, if the process be severe, rest in bed. Sufficient ventila-

tion without exposure of the patient to draft is a necessity. In general, the temperature of the sick-room should be kept as near 60° F. as possible. When the patient is aged, or in the case of capillary bronchitis in children, a higher temperature, even to 80° F., is sometimes desirable. In capillary bronchitis, too, the air of the room should be kept moist by the evaporation of water, on which aromatic or terebinthinate substances—**eucalyptol**, **menthol**, **benzoin** (preferably the compound tincture), etc.—may be thrown, so that their vapors may be pleasantly and equably diffused. Or, a “**croup-tent**” may be placed about the patient’s bed, and the air within it be moistened and medicated.

In many cases, the **open air** is better than any room. The roofwards of hospitals show an exceptionally low mortality. Especially is the open air of roof, porch, or tent desirable in cases of tuberculosis, and hardly less so in influenza. The patient’s head and body should be kept warm, however, by coverings adapted to the weather, and if necessary by hot-water bottles in the bed.

Hot flaxseed poultices applied over the affected area, or, when the process is widespread, over the entire chest, front and back (jacket poultice), are of great service. The poultice should be well made by slowly stirring boiling water into successive portions of flaxseedmeal, and the mixture should then be spread between two layers of cheesecloth. Oiled silk should be applied over the poultice, and the whole kept in place neatly by pins or bandage. Well made, properly applied, the poultice should retain its heat from four to six hours. From two to three poultices are to be applied during the day, and

“at bedtime” the skin is to be well dried and sponged with alcohol and alum, and the chest enveloped in a jacket of lambs’ wool. The following day and the third day, if necessary, the poultices are reapplied, the lambs’ wool being again substituted at night. It is rarely advisable to continue poulticing longer than this. In some cases poulticing may be preceded by counterirritation. The best method of counterirritation is by means of a mild **mustard plaster**, made with the addition of glycerin and white of egg. This can be retained in position for an hour or two without bad effect. In children it is better to rub the chest with amber oil night and morning, or a modification of St. John Long’s liniment may be used; for example:—

R *Amber oil*,
Oil of turpentine,
Oil of eucalyptus,
Oil of wintergreen,
of each ½ fl. oz. (15 c.c.).
Linseed oil 1 fl. dr. (4 c.c.).
Olive oil ½ fl. oz. (15 c.c.).
Vinegar 1 fl. oz. (30 c.c.).
Yolk of 1 egg.
Water, sufficient to
make ½ pt. (240 c.c.).

Sometimes the lambs’ wool or cotton jacket may be applied immediately, or following upon the counterirritation without the use of poultices. Considerable pain in the chest, widespread, or massive, consolidation or blocking of the air-vesicles constitute the indication for the use of poultices. In tuberculous cases, and when for any reason poulticing cannot be properly carried out, **dry heat** by means of hot-water bag, salt-bag, electric heating pad, etc., or **moist heat** by hot compresses may be substituted. The **application of ice to the chest** is strongly urged by some writers, cases of both croup-

ous and catarrhal pneumonia being included in their reports, which are exceedingly favorable. I do not employ the ice-pack in bronchopneumonia; but in tuberculous cases when the temperature exceeds 100° an ice-bag or a cold precordial coil should be applied over the cardiac area.

Study of means other than the internal use of drugs based on over 600 cases in infants and young children. Very few cases are primary, while the most serious of the causes of secondary pneumonia are diphtheria and measles. As the disease has no limit, runs no cycle, the preservation of vital resistance by not upsetting the stomach and disturbing the child is of great value. Little irritability, restlessness, or loss of sleep should be permitted. Good ventilation of the sick-room is essential; the temperature should never pass 70° F. (21.1° C.), and a flannel undershirt alone is advised. The writer never used a cotton jacket. The child is kept in his crib, water is given between nursings, and the time of nursing is decreased, while the food is diluted. The bowels must be moved once a day. The child should not be needlessly disturbed, food and medicine being given at three-hour intervals. **Steam inhalation with creosote** (10 drops—0.6 c.c.—to 1 quart—960 c.c.—of water) under a croup tent, for thirty minutes every three hours, advised, admitting fresh air every ten minutes. With much catarrh he used **turpentine** ($\frac{1}{4}$) with oil (%), but **mustard applications** make the best counterirritation. The boundaries to be covered should be marked out, and the plaster is to be made with 1 part of mustard to 2 parts of flour, applied for ten to fifteen minutes once in six to eight hours. Later applications should be weaker. They are especially effective at the onset, as are **mustard baths**, especially in cases with marked prostration. Drugs internally are only indicated symptomatically, and great care is necessary not to disturb digestion. Expectorants are best given in

powder or tablet form, dissolved in water, after feeding. The **ammonium salts** are only given during resolution, in $\frac{1}{2}$ -grain (0.03 Gm.) doses, and antipyretics are used only when the baths are badly borne. If there is much restlessness, **Dover's powder** may be given, watching its effect on the bowels. Heart stimulants are, as a rule, used far too early, but are needed when the pulse becomes soft, rapid, and irregular—such as 150 during sleep. He considers **tincture of strophanthus** best, but **strychnine** is also good when pushed to full doses or till some result is noted. **Digitalis** upsets the stomach easily; **whisky** or **brandy** is rarely needed and is best employed late, when other stimulants fail. **Nitroglycerin** may be used, but frequently causes headache. A daily **sponge bath** is advised, and when the fever reaches 104° F. (40° C.) a sponge or a cold pack is to be given. For the sponging, salt (3j—4 Gm.—to a quart of water) or alcohol (1 to 4 parts of water) is used. This is done under a blanket, the water being gradually reduced to 80° F. (26.7° C.), continued from ten to fifteen minutes. Too frequent sponging tires the patient. Cold tub baths have a very slight and temporary effect on this condition. He considers the **cold pack** the best hydrotherapeutic measure, given by using a large bath towel, the entire body being covered to the knees. Warm water is first used, decreased gradually by sponging. The temperature is taken in a half-hour. Children may be turned from side to side and enjoy the cool pack. An ice-bag is applied to the head; hot-water bags to the feet. **Oxygen**, given for one-half minute every half-hour, is also of value. C. G. Kerley (Phila. Med. Jour., May 16, 1903).

Few physicians are acquainted with the excellent properties of **mustard** as a counterirritant in the treatment of bronchopneumonia in infants and children. For the past thirteen years the writer and his colleagues have been using a method devised by him, with great advantage, which he de-

scribes as follows: 250 c.c. (half a pint) of water and 250 c.c. (half a pint) of alcohol are mixed in a large bowl; to this are added from 25 to 30 c.c. ($\frac{1}{2}$ to $1\frac{1}{2}$ ounces), according to the severity of the case, of freshly prepared spirit of mustard. The spirit of mustard is prepared according to the German Pharmacopeia (the volatile oil is the active principle of mustard) as follows: Oil of mustard, 1 part; pure alcohol, 49 parts. A large piece of flannel is moistened with the mixture and wrapped around the child from the neck to the knees. The child is then enveloped in a dry sheet and the pack is left on until the skin is a bright red, usually in from fifteen to thirty minutes. The child is then taken out and wrapped and left for another half-hour in a pack wet with 1 part alcohol and 2 parts water. At the end of this time the child is wrapped in a dry sheet. Usually one pack causes marked improvement, but relapses are frequent, and it may need renewal. Once in twenty-four hours is enough unless the indications are unavoidable. The physician should apply the first pack himself, to determine the strength needed and to instruct the parents or nurse. The advantages of the method are as follows: 1. It is surprisingly rapid in effect. 2. Its light weight does not materially embarrass respiration. 3. It can be applied without removing the enfeebled patient from the bed. 4. It is inexpensive. 5. It is clean. A. A. Herzfeld (Jour. Amer. Med. Assoc., Jan. 9, 1909).

Sponging the entire body twice daily with tepid water and aromatics or alcohol adds greatly to the comfort of the patient. Should the temperature be high, cool sponging, the cold pack, constant cool compresses, or the bath may be used. There must not, however, be any sudden shock in the latter case. The child should be plunged in water at 95° F., gradually reduced to 80° during the first bath. Friction should be used and

the duration of the bath be from eight to ten minutes. Subsequent baths with successively lower initial temperatures not falling below 80°, and final temperatures not falling below 70°, may be given at intervals of about four hours, whenever the temperature exceeds 104° F. Sometimes, especially with delicate or much depressed children, or the aged and feeble, **hot applications** (sponging, packing, or plunging, according to circumstances, of which the age and general reaction of the patient are the most important) are to be preferred. The effect upon general comfort as well as upon temperature must be considered. In cases of meningitis or with severe cerebral symptoms, an **ice-cap** should be applied to the head. Antipyretic drugs should never be given.

The following measures are recommended for infants: At the very first onset of pneumonic symptoms—high temperature; diminished resonance; small, non-crepitant or crepitant râles; apathy; increased rate of heart beat and respiration—the writer gives a bath of 86° F. (30° C.) for two minutes and then slowly reduces the temperature of the bath by adding cold water for from two to three minutes till a temperature of 76° F. (24.6° C.) is reached. The body of the patient is rubbed with a sponge, or cloth, or the hand to promote reaction of the skin and reduction of the body heat. The bath water need not, and in cases of feeble children should not, quite cover the body, but the water can be sponged on the chest, the patient lying in the arms of an attendant. If definite pneumonic symptoms be present the bath may have to be repeated at intervals of from eight to twenty-four hours. The **cross-packs** relieve the symptoms of bronchitis. The writer uses them extensively in incipient phthisis, but they give excellent results, and naturally prompt ones, in uncomplicated single bronchitis. They are applied in the following way: A linen

bandage about one and one-half inches broad for infants and five inches for adults, and from two to three yards long, is placed in cold water (from 54° to 66° F.—12.2° to 19° C.), is well wrung out, and is applied to the chest thus: (1) beginning under the right axilla, passing over the left clavicle and round the back to the right axilla; (2) from here round the chest horizontally; (3) from the right axilla to the left and over the back and the left clavicle to the front (or left axilla). This bandage is covered in the same way with a thick single or thin double flannel bandage perhaps half an inch broader. This "pack" is applied at night and left till the morning; on removing it the chest must be well rubbed with a cold, wet towel, and then rubbed dry. T. Zanger (*Lancet*, June 28, 1902).

Outline of treatment: **Castor oil** to clear the field of operation. **Fresh air, water**, plenty, inside and outside. Temperature of the water as indicated by child's temperature. Quiet and rest. Tranquilizing influences about patient. Undisturbed sleep. **Correct feedings** to avoid fermentation and gas in abdomen. If there is need, **high hot salines**. **Antipyretics**. Water. No coal-tar products. **Heart stimulants**. Fresh air. **Hot foot baths**. Relieving tympanites and crowding. Hot foot baths and hot salines can be given in a cold room. Both can be given under the bed-clothes. **Whisky and strychnine**. W. P. Northrup (*Med. News*, April 30, 1904).

In 31 cases the writer used a **vaccine** made from the mixed sputa of 20 patients with influenzal bronchopneumonia. The results were very encouraging. He sterilizes the pyovaccine, as he calls it, in the autoclave. *Pari* (*Gaz. degli ospedali e delle Clin.*, Feb. 2, 1919).

In acute bronchopneumonia complicating chronic pulmonary tuberculosis, a **cold application** may be made over the heart, as stated, whenever the temperature shows a tendency to exceed 100° F. The application should be continuous until the temperature

declines, and should be repeated according to necessity. Should this fail to bring the temperature to or below 100° F., **nitrogen monoxide**, about 8 gallons daily, should be given by **inhalation**. As the rise in temperature is usually postmeridian, the inhalation should be given in the forenoon, 4 gallons being administered at about 9 o'clock and 4 at about 11 o'clock. This will also conduce to sleep at night.

Food should be given as in fevers generally, in small quantities, at intervals of two or three hours, and should consist of easily assimilable and concentrated nutriment, pancreatized milk, beef-juice, egg-albumin, soft-boiled eggs, and the like. Children, the aged, and tuberculous patients are usually benefited by alcohol in small quantities, given with the food. The patient should be encouraged to drink water freely, so as to keep up to, or, better, beyond, normal the quantity of urine excreted, and it is usually well to give a mild alkaline diuretic, as solution of **potassium citrate** or solution of **ammonium acetate**.

If there is any tendency to constipation, or any failure of daily action of the bowel, **calomel**, **alkaline laxatives**, **glycerin suppositories**, or **enemata** should be employed according to circumstances. It is advisable to begin treatment with the administration of **castor oil** (perhaps with an equal quantity of **aromatic syrup of rhubarb** to make it palatable) or of **calomel** in divided doses.

No specific is known; but it is possible that so-called vaccination, especially with the **mixed bacterins** now available (and **tuberculin** in tuberculous cases), may soon be developed to the point of specificity.

Case of a girl of 8 who developed bronchopneumonia in the course of whooping cough. It persisted extremely grave for 5 months and then subsided completely. The child required **oxygen** daily for more than 2 months. Recurring spinal pains were relieved by **reclining on a hard bed**. Vomiting and anorexia hampered nutrition, but on milk, soups, lightly alcoholized fluids, eggs, etc., strength was regained. Garragan (Arch. Latina-Amer. de Pediatria, May-June, 1918).

The general medication should be adjusted to the individual case, and modified from time to time according to circumstances. There are many available agents, among which intelligent choice is to be made. **Quinine** given in large doses, especially the double hydrochloride of quinine and urea injected intramuscularly, is of great service in croupous pneumonia, and hardly less so in bronchopneumonia.

The writer reports his experience of seven years, in the Amer. Jour. Med. Sci., Jan., 1912. A 25 to 50 per cent. solution in sterile hot water is injected deeply into a muscle, through skin previously painted with tincture of iodine. Care is taken to empty the syringe before withdrawal, to avoid dropping solution upon the pierced skin, and the point of puncture is sealed with collodion or iodoform-collodion. For a robust adult the initial injection is 1 Gm. (15 grains) to 1.6 Gm. (25 grains); for aged persons 0.6 Gm. (10 grains); for children about 0.032 to 0.065 Gm. ($\frac{1}{2}$ to 1 grain) for each year of age, taking the vigor of the child and the severity of the case into consideration. The dose is repeated every three or four hours so long as the temperature shows a tendency to remain above

102° F., unless cinchonism develops. Sometimes only a single injection is made. Sometimes several injections are made daily for two or three days. The entire result must be considered. The drug may be given by the mouth when injection is not practicable. At the outset in the aged, and in feeble children, **strychnine** should be given in doses of about $\frac{1}{120}$ grain (0.0005 Gm.) to $\frac{1}{250}$ grain (0.0002 Gm.), repeated at intervals of from one to six hours, according to age and effect. It is not well to make a profound impression with the drug, or the patient's recuperative force will be exhausted. A gentle and continuous support of the vital powers is the object aimed at. For emergencies **strychnine** may be given hypodermically in doses to suit the occasion. Should cardiac or respiratory debility become alarming, strychnine should be supplemented by **atropine** [$\frac{1}{2000}$ to $\frac{1}{200}$ grain (0.00003 to 0.0003 Gm.), by skin or by mouth, every hour or at longer intervals, according to age and condition] or by **camphor**, which in children usually acts effectively when given as spirit of camphor by the mouth, in appropriate dosage: from 1 to 10 drops (0.06 to 0.6 c.c.); to an infant, $\frac{1}{4}$ drop (0.015 c.c.) in hot water. To an adult, **camphor** should be given hypodermically, dissolved in sterilized olive oil, 1 to 10; one, two, or three syringefuls of 20 to 30 minims each may be given, as needed, or the solvent may be half ether and half oil. Hypodermic injections of **ether**, with or without **camphor**, are sometimes useful. **Cocaine hydrochloride** [for an adult, $\frac{1}{2}$ grain (0.03 Gm.) hypodermically *p.r.n.*] is useful to relieve dyspnea and to sustain blood-pressure.

When quinine injections are used

cocaine should be given conjointly. The indication is a tendency for systolic blood-pressure measured in millimeters of mercury to fall below pulse rate measured in beats per minute. In a grave emergency, intravenous injection of a sterile solution of the **adrenal principle** might be serviceable. To children **alternate hot and cold douches** may be applied. The **ammonium preparations** are useful in nearly all cases. The aromatic spirit of ammonia, ammonium carbonate, ammonium chloride, or ammonium salicylate may be chosen. A good formula for an adult consists of:—

R <i>Ammonium chloride</i>	10 grs. (0.6 Gm.).
<i>Ammonium carbonate</i>	5 grs. (0.3 Gm.).
<i>Fluidextract of coca</i>	1 fl. dr. (4 c.c.).
<i>Spirit of nitrous ether</i>	20 min. (1.25 c.c.).
" <i>Essence of pepsin</i> " (neutralized)	1 fl. dr. (4 c.c.).
<i>Water</i> , or <i>Solution of ammonium acetate</i> , sufficient to make	½ fl. oz. (15 c.c.).

Dose: Tablespoonful (½ fluidounce—15 c.c.) every two, three, or four hours. The mixture will be turbid, and it may be necessary to "shake."

The coca in this formula, while it is useful as a heart tonic and diuretic, is used primarily merely to disguise the ammonium taste, and the pepsin preparation helps the stomach to bear the medicine. If pleurisy exists, **ammonium salicylate** may be added to this mixture. Another useful method of giving **ammonium carbonate** is to dissolve 5 or 10 grains (0.3 to 0.6 Gm.) in a dessertspoonful of **liquor ammonii acetatis**, and put this dose with

15 drops (0.9 c.c.) of **glycerin** and a dram or two (4 to 8 c.c.) of **sherry wine** in a wineglassful of cracked ice. Sometimes **egg-albumin** may be added. The whole can be swallowed at a gulp, and will often be retained without disturbance of the stomach when the drug cannot otherwise be given.

Opium need not be given except there be urgent indication to relieve pain or quiet excessive unproductive cough. It should then be used with circumspection. **Codeine** is usually the best preparation, but, if preferred, the **deodorized tincture of opium** or the **camphorated tincture of opium** may be added to the **aromatic spirit of ammonia** or other ammonium preparation employed. With children, **paregoric** is usually the best form in which to give opium.

In cases of continued weakness of the heart not sufficiently urgent to call for the hypodermic use of **camphor**, **tincture of digitalis** or Merck's German **digitalin** or other trustworthy digitalis preparation may be used in such doses and such manner as will produce the effect desired. **Caffeine** may also be used for more immediate effect, as digitalis is slow, but not always sure. When there is a tendency to edema of lungs and skin, **belladonna** or **atropine** may be associated or alternated with the digitalis or caffeine. **Strophanthus** is available sometimes, when digitalis fails. In tuberculous cases, especially those with high fever, **digitalis** may be employed in fairly large doses, as urged by Beddoes, and this use of it sometimes seems to be followed by the happiest results. From 20 to 30 drops (1.2 to 1.8 c.c.) of a good tincture may be given to an adult from three to six

times a day, until the pulse is reduced to 60 beats per minute; after which sufficient is given, the stomach permitting, to keep the pulse rate in the neighborhood of 70.

In children, and especially if the symptoms be those of suffocative catarrh, it is well to cause occasional emesis, for which purpose **syrup of ipecacuanha, alum in syrup of ipecacuanha or in honey**, or, if these fail, **apomorphine** may be employed. **Turpeth mineral** has been commended, but I have never used it. Following the emesis there is sometimes much prostration. I have found the inhalation of **amyl nitrite**, cautiously administered, of great service at this time, and also when suffocation cannot be relieved by emesis. In such cases, too, some more active expectorant than the **ammonium preparations** may be continuously necessary, and **syrup of senega, squill, or ipecacuanha** may be used. In mild cases a useful mixture is made with 5 to 10 minims (0.3 to 0.6 c.c.) each of **syrup of ipecacuanha, aromatic spirit of ammonia, and paregoric**, in water, which may be given every second or third hour.

In the bronchopneumonia of influenza in children the use of emetics is condemned as being a powerful factor in the production of pulmonary collapse and in the increase of the general prostration. Indication is to use stimulating expectorants early, and to reanimate the innervating powers by means of **alcohol, caffeine**, and injections of **camphorated oil**. This treatment must be pursued energetically from the very onset of the attack. Clemente Ferreira (*Revue men. des mal. de l'enfance*, March, 1895).

The writer emphasizes the peculiar prevalence and dangers of bronchopneumonia in children under 2, especially when the child is inclined to rachitis or digestive disturbances.

The younger the child, the graver the prognosis, in contrast to croupous pneumonia, which, he states, scarcely ever terminates fatally. Prophylaxis is particularly important, and there is hardly any other disease which can be warded off by proper hygiene so certainly as severe bronchiolitis and bronchopneumonia in young children. If whooping-cough and measles can be avoided until after the child is 3 years old and over, this is a great gain in the prophylaxis. He warns that pneumonia is unusually contagious for children with measles. The measles seems to enhance the susceptibility to diphtheria and tuberculosis and also for grippal affections and especially grippal pneumonia. Every person with influenza or even a mere "cold" should keep away from the young children in the family or institution. The writer insists on isolating away from young children every case of influenza in a hospital with as much care as the cases of measles and whooping-cough. Coryza in an infant should never be regarded lightly, and if pneumonia develops the infant must be taken to a hospital unless it can be well tended at home. Two rooms should be given up to it, changing several times a day from one to the other, while one is being aired and heated and the air moistened by hanging up wet sheets or boiling water in the room. The child's position in bed with shoulders raised should be frequently changed. In mild cases a **warm bath** twice a day, rubbing the arms and legs well, is soothing; in the severer cases the bath water must be heated from 37° to 40° or 41° C. by pouring in more hot water, rubbing the limbs, and keeping the child from six to ten minutes in the bath. The cough loosens up and the child sleeps quietly afterward. The hot bath draws the blood to the surface. Steam from boiling water generally serves to keep the cough loose, but if an expectorant is necessary he gives 10 drops (0.6 c.c.) three times a day of a mixture of

equal parts of **anisated solution of ammonia** and **fluidextract of senega**, say 10 Gm. (2½ drams), given in sweetened water. Heart tonics are more often needed than expectorants, and he prefers for infants 5 Gm. (1¼ drams) from three to five times a day of a 0.5 per cent. solution of **caffeine sodiobenzoate**, doubling the dose for children of 2 to 4. **Camphorated oil** in subcutaneous injection can be given from two to six times a day at need. In severe cases some of these tonic measures should precede each bath or mustard pack. Other measures that may prove useful are **inhalation of oxygen** or **atropine** to relieve asthmatic bronchitis; **potassium iodide** and, when rachitis impedes recovery, **phosphorus-cod-liver oil** may aid the cure. Feer (Jour. Amer. Med. Assoc., from Med. Klinik, April 21, 1912).

In influenza **salicin**, **sodium benzoate**, and **cinchonidine salicylate** are useful, and are to be associated with or substituted for other drugs mentioned.

In tuberculosis, **salicin** and the **guaiacol salts** (carbonate, cinnamate, and salicylate) are to be employed, or, if the stomach will bear it, **creosote** may be given. **Creosote carbonate** may often be given in large doses when creosote cannot be taken. **Creosote carbonate** is also useful in many non-tuberculous cases, especially when there is much cough and somewhat scanty expectorations. The best way to administer the drug is in hot milk. The dose [1 to 5 drops (0.06 to 0.3 c.c.) for a child, 5 to 15 drops (0.3 to 0.9 c.c.) for an adult, every two to six hours] may be floated on a tablespoonful of the milk and thus swallowed, after which from 2 to 6 ounces (60 to 180 c.c.) of unmedicated milk should be sipped slowly. It is usually well to alternate the creosote prepara-

tion with **salicin**, the **ammonium salts**, **ippecac**, **digitalis**, **belladonna**, or **strychnine**, as the case may be, when any of these drugs is indicated.

As recovery takes place, the medication, whatever it may have been, should be gradually withdrawn. Should resolution be sluggish, it is well to give **ammonium iodide**, preferably in a vehicle containing **pepsin**, and followed by a large draught of water. The dose should be small at first, 5 grains (0.3 Gm.) for an adult, and gradually increased. The application of **hot poultices** for a few days is again likely to be useful.

When recovery is unduly delayed the application over the affected areas of **mercurial ointment**, or of **iodine in lanolin** (20 grains—1.3 Gm.—to the ounce—30 Gm.), or in liquid **saponified petrolatum**, often seems to hasten it. The **iodine ointment** should be applied a few drops at a time, and well rubbed in until a dram (4 Gm.) or more has been taken up by the skin. A gauze dressing covered by oiled silk or rubber tissue should then be placed over the treated area. **Calomel** in small, frequently repeated doses for two or three days, just avoiding salivation, is not rarely useful at this time.

Should there be suppression of urine, bloody urine, or albuminuria, it is well to suspend all medication except some bland **alkaline diuretic**, and **take blood**, either from the arm or by **wet cups over the kidneys**, after which **warm** (100° to 104° F.) **physiological saline solution** should be introduced slowly, either by a vein or under the skin. **High irrigation of the colon with hot physiological saline solution** (110° F.) may temporarily substitute the venous or subcutaneous infusion.

The Murphy method of **continuous enteroclysis** may be employed in suitable cases. When the condition of the patient is markedly septic or toxemic, as shown by muttering delirium and general depression, the same measures should be used.

Leeching back of the ears may be the best method of depletion in cerebral cases. When the chief difficulty seems to be in the circulation, judgment must be exercised, in view of all the circumstances of the case, as to the employment of these measures. If one can be sure that the obstacle to circulation is not merely the weakness of the heart, but that the latter is simply an indication of peripheral difficulty, bloodletting by **wet cupping** over the chest or even by **venesection** is justifiable, and the introduction of **saline solution** may usefully follow. Sometimes the use of **nitroglycerin** internally suffices.

When the respiratory obstruction seems to be great, as shown by cyanosis, dyspnea, rapidity of breathing, short, hacking, incessant, unproductive cough, there is no measure so useful as the **inhalation of oxygen**. At first this must be as nearly continuous as possible. As improvement takes place, the intervals and duration of inhalations are modified accordingly. It is especially in children, in the aged, in cases following the exanthemata, and in septic cases generally that I have seen oxygen save life. But it will not revive the dead. If resort to it be too long delayed, or its administration be economical or timid, no good result is to be anticipated.

In bronchopneumonia in young children the writer gave large and almost continuous **inhalations** of pure **oxygen** as an antiseptic for the air passages. The therapeutic results were remarkable. Bronchopneumonia is a descending infection of the

air passages from infections of the nasopharynx, which are usually saprophytic. The lesion is treated locally by the oxygen, and at the same time the system is protected against the effects of the infection. A veritable atmosphere of oxygen is created for the lungs, the inhalations being repeated every hour or half-hour. Weill (Lyon méd., Jan. 2, 1910).

Convalescence must be skillfully managed to avoid the development of chronic bronchopneumonia, or the supervention of tuberculosis in non-tuberculous cases. **Food, fresh air, cold-water bathing, and friction of the skin**, with perhaps, in some cases, roborant medication by means of **iron, arsenic, calcium glycerophosphate**, and the like, and regulated **pulmonary gymnastics** meet the indications. In some cases, especially when scrofula exists or tuberculosis is suspected, the continuance of **creosote** or the administration of **guaiacol cinnamate** is necessary.

Chronic bronchopneumonia calls for good general **hygiene** and **nutrition**, the application of a series of small **fly-blisters over the chest** (about one inch square; one at a time; applied over a new area each time; with intervals of three or four days between applications), and systematic expansion of the chest by **inhalation of compressed air** or other efficient means. Internally iodine compounds are to be given. Pills or capsules of **iodoform**, or of iodoform and iron, or of iodoform, iron, and **arsenic** may be alternated with **ammonium iodide** or **syrup of hydriodic acid**. Small doses are to be given at first, and gradually increased to the point of tolerance. **Strychnine** and **calcium glycerophosphate** are useful tonics, and may be alternated with the doses of **iodoform**.

If the cases prove rebellious to any of the lines of treatment described above, a **sea-voyage** should be recommended, and, this failing, **change of residence**—temporary or permanent—to a cold, dry region, preferably at a considerable altitude, in the case of one young and robust; to a warm, but dry and equable region in the case of the aged.

SOLOMON SOLIS-COHEN,
Philadelphia.

BUCHU consists of the leaves of *Barosma betulina* or of *Barosma crenulata*, shrubs of the natural order Rutaceæ, native of South Africa. They contain a volatile oil which is doubtless the active principle and includes a camphor-like body, *diosphenol*; a bitter extractive, *barosmin*; a resin, a gum, and lignin. The oil has a peppermint-like odor.

PREPARATIONS AND DOSE.—*Fluid-extractum Buchu* (fluidextract of buchu).—Dose, 30 to 60 minims (2 to 4 c.c.), three times daily for an adult; 10 to 30 minims (0.6 to 2 c.c.) for a child. It should be well diluted before taking.

An infusion of buchu, unofficial, is also sometimes used. It is made by adding an ounce of the leaves to a pint of water. Dose, $\frac{1}{2}$ to 2 ounces (15 to 60 c.c.).

PHYSIOLOGICAL ACTION.—A sense of warmth is imparted to the stomach by small doses; this gradually diffuses over the body. The pulse rate is increased, appetite stimulated, and slight diaphoresis induced. The drug increases slightly the flow of urine, which tends to become dark in color, acquires a strong aromatic odor, and may deposit a brownish sediment. The urine is rendered slightly antiseptic by buchu. Large doses produce vomiting, purging, and strangury, with a burning sensation in the stomach.

THERAPEUTIC USES.—Buchu is used in chronic catarrhal conditions of the genitourinary tract. The oil acts as a stimulant to the mucous membranes of the kidney and the genitourinary passages, and also exerts an alterative effect on them if diseased. It is thus a useful remedy in chronic pyelitis, subacute and chronic

cystitis, vesical irritation (especially of the neck of the bladder), prostatitis, and urethritis. The drug has also been administered in chronic bronchitis, chronic rheumatism, atonic dyspepsia, lithiasis, affections of the skin, and dropsy. W.

BUERGER'S DISEASE (Thromboangiitis obliterans).—A condition which may be mistaken for Raynaud's disease has been described by Leo Buerger, of New York, under the term *thromboangiitis obliterans*. It occurs usually in male Russian Jews of middle age, and is believed by Buerger to be due to acute inflammatory lesion and consequent occlusive thrombosis of arteries and veins, the lesion involving deep veins in about 40 per cent., and the superficial veins of the upper and lower extremity in 20 per cent. of the cases. The symptoms consist of pain in one foot or lower extremity, the opposite limb becoming involved later in some instances. There is tenderness of the calf muscles, and the great toe often exhibits a dusky red color, which may disappear upon elevation of the limb. There may be tickling or burning sensations in the part. Pulsation in the arteries of the foot and leg may be impalpable. When the patient attempts to walk any distance, the phenomena of intermittent claudication are likely to set in. According to MacCallum, the lumen of involved vessels in these cases is found to be filled with vascular granulation tissue, sometimes with endothelium-lined spaces, through which a little blood may flow. The ultimate consequences may be ulceration and gangrene of the toes or of the whole foot or leg. During the earlier stages relief from the constant pain is sometimes obtainable by allowing the foot to hang down. Application of heat may also give temporary comfort.

W. A. Steel (Trans. Phila. Co. Med. Soc.; Med. Rec., Feb. 26, 1921) employed the following method of treatment for the past 3 years, with encouraging results: During the first month the patient is kept in bed with the legs constantly in either a hot air or electric light bath at 110° F., and 250 c.c. ($\frac{1}{2}$ pint) of 2 per cent sodium citrate solution is given intravenously every second day. During the second

month the interval of injection is lengthened to every third or fourth day, daily leg **massage** is given and the patient put in a wheeled chair with feet hanging down for a short time each day; or, if the case is not advanced, some walking is allowed. The intervals of injection are then gradually lengthened until 1 is given every 2 weeks. **Potassium iodide** in 10-grain (0.6 Gm.) doses 3 times daily is given during the whole course of treatment. S.

BULBAR PARALYSIS.—Two types of this disease have been recognized: ACUTE BULBAR PARALYSIS, or ACUTE INFERIOR POLIOENCEPHALITIS, rarely observed, in which there occurs rapid or sudden involvement of the lower portion of the bulb, or medulla oblongata in the course of certain infectious diseases and other toxemias, and CHRONIC (PROGRESSIVE) BULBAR PARALYSIS, or LABIOGLOSSOLARYNGEAL PARALYSIS, in which there occurs progressive paralysis of the tongue, pharynx, and larynx as a result of various factors, prominent among which are syphilis, Bright's disease, also some diseases of the spinal cord, such as amyotrophic lateral sclerosis, multiple sclerosis, syringomyelia, tabes.

ACUTE BULBAR PARALYSIS.

SYMPTOMS.—The onset is characterized by the usual signs of an infectious invasion, viz., headache, vertigo, chills, and fever. Rapidly a paralysis of the muscles supplied by various bulbar nerves makes its appearance. The tongue, lips, palate, and larynx are first affected. Sometimes the muscles of the face and the external recti muscles of the eyeballs are involved. The inability of retaining food in the mouth, the difficulty of swallowing, the projection of liquids and food through the nose during the attempts at swallowing, the nasal in-

tonation of the voice, the difficulty of breathing—are all the characteristic clinical manifestations of the disease. Its course is usually rapid; it lasts but a few days. In exceptional cases, however, it may be prolonged to a few weeks. The outlook is always grave. Death is usually the result of suffocation. Occasionally recovery has been observed (Eisenlohr). The writer observed an almost complete recovery in a case of acute bulbar palsy occurring in the course of diphtheria in a girl of 14 years.

Case of acute bulbar paralysis in a man of 62 who had been previously healthy except for occasional migraine. Then he had an attack of dizziness and vomiting for nearly 2 days but no headache or other symptoms. The next day he found he could not swallow. The whole act of swallowing was paralyzed. He learned to feed himself through a stomach tube and after several months a faint tendency to return of the ability to swallow is now evident. L. Nicolaysen (Norsk Mag. f. Laeger., Apr., 1918).

DIAGNOSIS.—The above symptoms and their sudden or rapid onset are so characteristic that the disease can be easily recognized. Some difficulty, however, may be experienced in differentiating it from sudden "pseudobulbar palsy." But in the latter affection the symptoms of muscular paralysis are much milder than in the first; besides, in most cases there are usually two distinct attacks, and only the last produces a distinct paralysis of the lips, tongue, and pharynx. Finally, in pseudobulbar palsy there are always indications of a lesion in one or the other hemisphere, such as hemiplegia.

ETIOLOGY AND PATHOLOGY.

—Acute bulbar palsy has been observed in the course of infectious diseases,

such as diphtheria, scarlet fever, pneumonia, and typhoid fever. Grave alimentary intoxications may also be followed by acute bulbar symptoms. The disease may occur in chronic alcoholism and in syphilis.

The lesion consists of foci of hemorrhages or softening. The gray matter, the white matter, and the nuclei of the bulbar nerves may be simultaneously affected. The maximum of involvement is at the level of the nuclei. All the nerves, except the third, fourth, and the sixth, may be affected. Sometimes a combined, viz.: an inferior and a superior, polioencephalitis is observed. In such cases the nerves of the upper and lower portions of the medulla are simultaneously involved. Microscopically the medulla appears in a state of inflammation, to wit: the blood-vessels are dilated, congested; the perivascular spaces are filled with leucocytes; the cells of the nuclei are in a state of chromatolysis, and the axis-cylinders undergo degeneration. In Eisenlohr's case taken from a typhoid-fever patient who died with symptoms of acute bulbar palsy, microbes were found in the medulla. Gerson recently (1916) observed 2 cases of myasthenic bulbar paralysis due to diphtheria. The symptoms appeared at intervals, beginning with progressive weakness of the muscles of the lips and tongue and of the facial muscles.

TREATMENT.—Counterirritation applied to the neck and purgatives are the immediate means. Special attention must be paid to the feeding. In view of the difficulty of swallowing, the patient is in constant danger of suffocation. When a history of syphilis is obtained, injections of **salvarsan** may be tried.

CHRONIC (PROGRESSIVE) BULBAR PARALYSIS, OR LABIOGLOSSOLARYNGEAL PARALYSIS.

SYMPTOMS.—The onset is slow, but progressive. It is usually preceded by some vague pain in the neck. Gradually a weakness of the tongue is noticeable. The patient experiences some difficulty in moving it in the mouth during the act of mastication or in speaking; also in protruding it. At the same time or shortly afterward the lips become affected. The palate follows next in order. Finally, the muscles of the pharynx and the larynx become involved.

When the disease is at its beginning, the striking disturbance is in the tongue. The letters which require the use of the tongue are poorly pronounced; the speech is indistinct (dysarthria). In a more advanced period of the disease not only marked limitation of movements of the tongue is observed, but the organ appears flat and flabby, it is atrophied, and fine fibrillary contractions are noticeable. At this stage the speech is almost impossible (anarthria). Reactions of degeneration are present. Mastication is very difficult, and the food remains a long time in the mouth. The muscles of the lips undergo atrophy, and the patient is unable to execute the act of blowing and whistling. During the act of speaking they remain immobile. The mouth is open, and the saliva is continuously dribbling. The facies is then characteristic. It gives the impression of mental hebetude, and this is particularly noticeable in the act of laughing. The patient does it with a widely open mouth and for a sufficiently long time to impress as being stupid. A tendency to keep on laughing when once started is somewhat

characteristic of the disease. The silly facies is only apparent, as in reality there is complete preservation of mental faculties.

The condition of the muscles of the lips increases the difficulty of speaking and especially in pronouncing labial letters. Fibrillary contractions and reactions of degeneration of the muscles of the lips are present.

The paralysis of the palate is manifested by the nasal intonation of the voice; in order to improve the pronunciation the patient closes up his nostrils, so that the air during the act of speaking passes entirely through the mouth. When the pharynx becomes involved, the patient's deglutition is embarrassed. The food is rejected through the nose and the mouth. The patient uses all sorts of subterfuge to force the food into the pharynx: he throws his head backward; sometimes pushes the food with his fingers. He is in constant danger of having particles of food penetrate into the larynx.

The involvement of the larynx is a late manifestation. In such a case speech is absolutely impossible and aphonia is complete. Besides, the danger of suffocation from food is greater. Bronchopneumonia from aspiration of particles of food into the larynx is not rare.

The involvement of the nuclei of the most important nerves naturally leads to cardiac and pulmonary complications. The latter have been already mentioned. It may, however, be added that the inability of the patient to breathe or expectorate properly leads to accumulation of mucus in the bronchial tubes, so that an ordinary bronchitis may be very serious. As to the cardiac disturbances, they consist of attacks of cardiac oppression, of attacks of syn-

cope; the pulse is small, feeble, and irregular.

Case of chronic bulbar paralysis of diphtheritic origin in a male patient of 24 years who presented considerable atrophy of the tongue, with fibrillary tremors, almost complete laryngeal paralysis, and atrophy of the vocal cords. These symptoms came on gradually one after the other after a severe attack of diphtheria at the age of 12 years, which affected both the pharynx and larynx. The more immediate paralysis of the soft palate disappeared, but the laryngeal paralysis became accentuated. The condition of the tongue came on some time afterward, and one could actually observe, in addition to the laryngeal and lingual affections, a slight paresis of the lips on the right side, and a distinct diminution in the hearing power. It seemed, therefore, as if there were here present a progressive lesion of the bulbar nuclei, due to the influence of the diphtheritic toxin. Siredey (*Le progrès méd.*, Nov. 24, 1906).

Among other symptoms of labioglossolaryngeal paralysis may be mentioned the increase of the patellar tendon-reflexes, which has been observed in the majority of cases, although not in all. This fact speaks in favor of the view that progressive bulbar paralysis is a form of amyotrophic lateral sclerosis (see Pathology).

Progressive bulbar palsy may sometimes develop in the course of progressive muscular atrophy. It is then an indication that the pathological process of the latter disease, which consists of a progressive destruction of the cells of the anterior cornua of the cord, has reached the medulla and involved the cells of the nuclei.

When, in the course of such cases, the progressive muscular atrophy is at its climax, a gradual involvement of the lips and tongue begins to be noticeable.

DIAGNOSIS.—There is no difficulty in recognizing the affection from its slow onset, gradual and progressive involvement of the muscles of the tongue, lips, pharynx, and larynx. However, a difficulty of swallowing, of opening the mouth, of moving the tongue may be encountered in acute tonsillitis or pharyngitis. In the latter affections there will always be fever, pain, adenopathy, which are wanting in bulbar palsy.

Bilateral facial paralysis may simulate progressive bulbar palsy through the immobility of the facies, but it should be borne in mind that in the latter affection the upper part of the face is not involved and in the first affection the muscles of the tongue, larynx, and pharynx are not involved.

Difficulty of deglutition, nasal intonation of the voice may be caused by paralysis of the palate in the course of or following diphtheria, but there is no involvement of the tongue or lips.

Pseudobulbar palsy always follows one or two apoplectic seizures. The symptoms of bulbar paralysis are only slightly marked after the first attack, but are distinct after the second attack. However, there is no slow, progressive, and successive involvement of the tongue, lips, and pharynx. Besides, there is always present a hemiplegia. The muscles affected do not show reactions of degeneration or fibrillary tremor. Intelligence is diminished, and there is a spasmodic laughing or crying.

In myasthenia gravis there is a weakness of the muscles of the tongue, larynx, palate, and pharynx, but there is a predominance of weakness in the masticatory muscles and in the levator palpebræ. Ptosis is evident. Besides, the general asthenia, the absence of atrophy, of reactions of degeneration,

of fibrillary tremor, the presence of the special myasthenic electrical reaction consisting of rapid exhaustion of muscular contractions—are all sufficient to distinguish this affection from progressive bulbar paralysis.

ETIOLOGY.—The true causes of the disease are not known. It has been observed in the course of amyotrophic lateral sclerosis, progressive muscular atrophy, syringomyelia, tabes, multiple sclerosis. Debilitating diseases, syphilis, intoxications, exposure to cold, overuse of the muscles have been mentioned by various authors as causes of the affection. It usually occurs in middle age, although it has been observed in children. Males are more frequently affected than females.

PATHOLOGY.—The morbid changes consist chiefly of a primary, but progressive degeneration of the nuclei of the nerves originating in the lower half of the medulla—viz.: in the nuclei of the seventh, ninth, tenth, eleventh, and twelfth nerves. The most marked changes are seen in the nucleus of the twelfth nerve. These changes are similar to those observed in the cornua of the spinal cord in progressive muscular atrophy. They show various stages of chromatolysis with subsequent disappearance of the cells. The axicylinders emanating from these cells and the roots of the nerves undergo degeneration. The interstitial tissue is also changed; sometimes there is an increase of connective tissue and thickening of the walls of the blood-vessels.

The pathological process may not be confined exclusively to the nuclei. Not infrequently the white matter of the medulla has been found affected. Degenerative changes in such cases have been traced in the pyramidal bundles through the pons and cerebral pedun-

cles. Otherwise speaking, progressive bulbar paralysis may be an amyotrophic lateral sclerosis. Leyden believes that this is always the case; Raymond, Déjerine, and others admit that, while an involvement of the white matter is a frequent occurrence, nevertheless, an independent nuclear involvement, such as Duchenne originally described, is also possible.

The muscles in which the degenerated bulbar nerves are distributed undergo atrophy. Their size is diminished; the nuclei of the sarcolemma proliferate; the interstitial and fatty elements are increased. The muscles affected are those of the tongue, lips, pharynx, and larynx.

PROGNOSIS.—The disease is essentially progressive. Remissions, or temporary arrests of development, are sometimes observed. It may last from a few months to several years. There are no cases of cure on record. Death may result either from inanition because of the difficulty or inability of swallowing, from bronchopneumonia caused by penetration of food into the air passages, or from sudden involvement of the heart in attacks of syncope. The prognosis is invariably grave.

TREATMENT.—There is no special medication that could arrest the course of the disease. Local **cauterization** of the neck, antisyphilitic remedies: **mercury**, the **iodides** and **salvarsan**, and also **strychnine**, **nitrate of**

silver, **arsenic**, **phosphorus**, **electricity** applied to the neck or to the affected muscles—may all be tried, but not much reliance can be placed on any of the remedies.

Case of bulbar paralysis, followed by progressive muscular atrophy, in which great benefit was undoubtedly obtained from the application on alternate days of **medicated electrodes**, with the patient placed on an insulating platform, the pad being connected with the positive side of a static machine, the negative pole of which was grounded. The dischargers were then arranged so as to give a powerful "Morton wave" current. In addition, local application of similar current was made by means of a glass vacuum electrode over the affected muscles and their motor points. The patient, notwithstanding the great symptomatic improvement in every way, died suddenly about three months later, without any evidence of pain or respiratory embarrassment. Little and Bokenhan (Brit. Med. Jour., Sept. 12, 1908).

When the patient has difficulty in swallowing, he must be fed through an esophageal tube. In case of suffocation, **tracheotomy** must be performed.

ALFRED GORDON,
Philadelphia.

BUNION. See **TENDONS**: **BURSITIS**.

BURNS. See **SKIN**, **SURGICAL DISEASES OF**.

BUTYL CHLORAL HYDRATE. See **CROTON CHLORAL**.

CACODYLIC ACID and its salts, the **CACODYLATES**, constitute a series of organic arsenic compounds containing the basic radical cacodyl $(\text{CH}_3)_2\text{As}$. Being at present used to a

considerable extent in medicine, sodium cacodylate has been officially recognized in U. S. P. IX as *Sodii cacodylas*.

The formula of cacodylic acid, or dimethylarsenic acid, is $(\text{CH}_3)_2\text{AsO}_2$.

OII. It occurs in the form of colorless, odorless crystals, with a slightly sour taste, and is soluble in water and alcohol. It contains 54.3 per cent. of elemental arsenic.

Sodium cacodylate $[(\text{CH}_3)_2\text{AsO} \cdot \text{ONa} + 3\text{H}_2\text{O}]$, now generally used in preference to the acid, is prepared by distillation of arsenic trioxide with potassium acetate, oxidation of the resulting products with mercuric oxide, and neutralization of the cacodylic acid thus obtained with sodium hydroxide. It appears as an amorphous, white powder, or crystals, easily soluble in water. The fluid resulting from its dissolution is alkaline in reaction toward litmus, but is practically neutral toward phenolphthalein. Sodium cacodylate, while chemically a stable substance when in the dry state, absorbs water from the air. When kept in solution, it tends to deteriorate after a time (Arnozan). It contains 36 per cent. of pure arsenic.

Sodium methylarsenate, or *arrhenal* $[\text{CH}_3 \cdot \text{AsO} \cdot (\text{ONa})_2 + 5\text{H}_2\text{O}]$, greatly resembles sodium cacodylate in action. It occurs as white crystals, readily soluble in water and slightly so in alcohol. It contains 33 per cent. of arsenic.

DOSE AND MODES OF ADMINISTRATION.—The dosage of cacodylic acid, sodium cacodylate, and sodium methylarsenate in adults ranges from $\frac{1}{4}$ to 2 grains (0.016 to 0.13 Gm.) per diem. In children 6 to 10 years old the maximal daily dose is $\frac{1}{3}$ to $\frac{1}{2}$ grain (0.02 to 0.03 Gm.), and in those 3 or 4 years old $\frac{1}{6}$ grain (0.01 Gm.) (Rocaz).

These drugs, though often used internally, are, in addition, especially suitable for hypodermic injection, causing no local irritation except in

large doses. According to Gautier, as much as $1\frac{1}{2}$ to 3 grains (0.1 to 0.2 Gm.) per diem will be retained by the stomach for an indefinite period. Administration of the drug by enema has also been carried out, $\frac{1}{10}$ to $\frac{1}{6}$ grain (0.006 to 0.01 Gm.) being given dissolved in water two or three times daily.

Renaut suggests the following solution for use by rectum:—

R. *Sodium cacodylate* ... 4 to 6 gr. (0.25 to 0.40 Gm.).
Water $6\frac{1}{2}$ oz. (200 c.c.).

M. Sig.: Use 80 minims three times a day.

Sodium cacodylate is in most cases well borne when administered by the mouth, and produces its usual therapeutic effects. Among 13 cases in which the drug was employed, many gained in weight, especially 4 with **phthisis**, 1 with **chorea**, and 1 with **Graves's disease**. In none was the garlicky odor present. In no case was there gastrointestinal disturbance. Improvement in appetite always preceded the gain in weight. The daily doses used varied from $\frac{1}{8}$ to $\frac{3}{4}$ grain (0.0216 to 0.048 Gm.). The treatment was continued for ten days and then interrupted. Brousse has used much larger daily doses (4 to 5 grains—0.26 to 0.32 Gm.) in dermatological cases without causing untoward effects. Grasset (*Semaine médicale*, No. 11, 1900).

Three cases of simple **chorea** of moderate severity in children aged, respectively, 8, 12, and 14 years in which sodium cacodylate was used with success. A rectal injection of 1 dram (4 Gm.) of cacodylate solution (1 to 400) was given daily for the first five days, twice daily for the next five days, and thrice daily for the next five days.

After an interruption of five days the treatment was repeated for fifteen days. There were no untoward effects. Belbèze (*Semaine médicale*, No. 13, 1900).

Experience with intravenous injections of a 5 per cent. solution of sodium cacodylate in over 400 cases showed that this method is as safe and reliable as the hypodermic—in fact, more so. The action is more prompt and certain. An ordinary hypodermic syringe suffices, but the strictest aseptic precautions are, of course, necessary.

Anemia, tuberculosis, diabetes, scrofula, nervous disorders, skin affections, and cancer were thus treated. Sometimes, as in **cancer of the breast, in sciatica, and in scrofula**, the remedy is best injected *in loco*. In **anemia and chlorosis** the results obtained were brilliant. Sometimes in four to six weeks a cure was effected. Sodium cacodylate was used, the initial dose being $\frac{5}{8}$ grain (0.054 Gm.) daily, increased up to $1\frac{1}{2}$ grains (0.01 Gm.) every second day. In severe cases the daily dose was about 3 grains (0.2 Gm.). After three weeks' treatment, a pause was made for a week, and the medication then resumed. Occasionally the remedy was given internally, in pills or according to the following formula:—

℞ Sodium cacodylate $\frac{1}{2}$ dr. (2 Gm.).
Rum,
Syrup, ..of each 4 dr. (16 c.c.).
Distilled water. 2 oz. (60 c.c.).
Peppermint oil. 2 drops (0.12 c.c.).
 (A teaspoonful contains $1\frac{1}{4}$ grains (0.081 Gm.) of sodium cacodylate).

In **tuberculosis** the success was very encouraging, especially in a case of **urogenital tuberculosis**. In **sciatica** and in **palsies** sodium cacodylate was given locally under the skin in doses of $1\frac{1}{4}$ grains (0.081 Gm.) with good results. F. Mendel (*Therap. Monatsh.*, Bd. xvi, Nu. 4, 1902).

PHYSIOLOGICAL ACTION.—

The effects of cacodylates are essentially those of arsenic, exerted more slowly owing to the fact that the arsenic does not develop its accustomed action until it has been liberated from the firm organic combination in which it is present in the cacodylic

compounds. Since this liberation takes place only in relatively small amount, Heffter's experiments having indicated that but 2 or 3 per cent. of sodium cacodylate is decomposed with liberation of the arsenous ion, the action of the drug is correspondingly weakened. The cacodylates have been claimed to be less toxic than inorganic forms of arsenic, and also to be less prone to cause unpleasant side-effects. It has not at all been clearly shown, however, that the degree of toxicity is any lower than one would naturally expect from the small percentage of arsenic liberated, *i.e.*, there is no reason to believe that the ratio of toxicity to therapeutic power is any lower than in the case of the inorganic arsenic compounds. Indeed, the fact that arsenic in free inorganic form appears to be the active agent in cacodylates as well would tend to suggest the impossibility of any such difference in relative toxic power.

Sodium cacodylate can be detected in the urine after hypodermic injection of daily doses of from 0.05 to 0.2 Gm. ($\frac{1}{2}$ to 3 grains) in from ten to thirty-six days or more. Inorganic arsenic began to be eliminated in 2 cases under observation after twenty-two and forty-four days, respectively. The amount eliminated was small and personal idiosyncrasy seemed to play a considerable part. In dogs injections of 0.33 Gm. (5 grains) daily for nine days caused no objective symptoms, but the drug was excreted on the second day and daily thereafter. Inorganic arsenic made its appearance in the urine on the twelfth day. No macroscopic pathological changes were found at autopsy, but inorganic arsenic was found in the muscles, liver, and bone-marrow. Only a small portion of the injected drug is eliminated through the urine. Whenever inorganic acid could be detected

in the urine it was also present in the feces. In a large rabbit killed by an injection of 1 Gm. (15 grains), the tissues, liver, and muscle had a garlicky odor and chemical analysis revealed inorganic arsenic. The authors feel sure that cacodylic acid, as well as inorganic arsenic, is deposited in the tissues. That large doses are required to produce effects is undoubtedly due to the fact that the drug is only partially decomposed to inorganic arsenic, and the benefit is to be ascribed to a self-regulation and automatic immunity which the organism acquires by the constant presence and new formation of arsenic of the inorganic type in the body. The production of arsenous or arsenic acid in a nascent state is probably not an unimportant factor; as in this condition even small amounts of the ions become more active and give better results than arsenic given as such *per os*. It is not impossible, however, that cacodyl or its oxide, which is also produced, may have an action of its own not unlike that of the inorganic arsenic compounds. Dawes and Jackson (Jour. Amer. Med. Assoc., June 22, 1907).

From both experimental work and clinical experience it has become clear that cacodylates exert effects on the blood and on general nutrition similar to those of inorganic arsenic. De Biehler found a distinct increase of body weight to occur in rabbits given sodium cacodylate over and above that taking place in the same period of time in control animals. The results obtained with cacodylates in cutaneous affections also suggest that their action on the skin is the same as that of arsenic in inorganic form.

Action of sodium cacodylate on the blood and on oxidation processes studied experimentally. Rabbits were given doses of 0.005 Gm. ($\frac{1}{12}$ grain), gradually increased to 0.01 or 0.015 Gm. ($\frac{1}{6}$ to $\frac{1}{4}$ grain), on alternate

days for two months. All the animals increased in weight by 300 to 400 Gm. (10 to 13 ounces) during this period, while the control rabbits increased only 50 to 100 Gm. ($1\frac{1}{2}$ to $3\frac{1}{2}$ ounces). The increase in weight was proportionate with the dosage. The specific gravity of the blood and the hemoglobin percentage were increased, while the number of red and of white corpuscles was diminished. The power of oxidation in the organism was lowered. Sodium cacodylate should therefore be prescribed only where there is excessive oxidation in association with decrease of albumin and hemoglobin in the blood. It is contraindicated in morbid states where oxidative processes in the organism are diminished. M. de Biehler (Arch. internat. de pharmacodyn. et de thér., vol. xvii, No. 112, 1907).

According to Dawes and Jackson, cacodylic acid is deposited in the body tissues, and then gradually in part decomposed. The amount of arsenic eliminated in the urine as the result of cacodylic medication was found to vary in different individuals, personal idiosyncrasy apparently playing a considerable part.

A pronounced garlic-like odor of the breath is frequently observed in those taking cacodylates, whether by mouth or hypodermic injection. This is believed due to the formation of the strongly smelling compound cacodylic oxide, by partial decomposition of the drug. One of Dawes's patients treated with sodium cacodylate reported the odor of garlic in the perspiration about a week after injections of 3 grains (0.2 Gm.) had been commenced. Complaint of the odor in the urine is not an infrequent occurrence; this odor may also be observed in inorganic arsenic medication.

UNTOWARD EFFECTS AND POISONING.—While cacodylic compounds were at first claimed to be “non-toxic” and devoid of the unpleasant collateral effects of inorganic arsenic compounds,—diarrhea, pigmentation of the skin, paralyses,—clinical experience with them has shown that this is only relatively true. Wm. Murrell has reported a case which shows that sodium cacodylate may produce all the untoward systemic effects of arsenic in a marked and decided manner: The patient was a young woman 21 years of age suffering from moderately advanced pulmonary tuberculosis, and was ordered 1 grain (0.06 Gm.) of a reliable preparation of the drug in pill form three times daily. On the following day there was a distinct odor of garlic on the breath, on the third day the patient vomited twice, and on the fourth, after 11 doses had been taken, she developed symptoms of arsenical poisoning. Her face was pale, the eyelids edematous, and the conjunctivæ injected. The patient suffered from constant nausea and vomiting, and complained of pains in the limbs, especially the lower. There was tenderness on deep pressure over the course of the nerves, and she was unable to move the left leg. There was distinct loss of power in the extensors of the left wrist. The patellar reflexes were preserved; there was no diarrhea or albuminuria. On suspending the treatment the acute symptoms subsided in twenty-four hours, but the loss of power in the leg and wrist persisted for some days.

THERAPEUTIC USES.—Sodium cacodylate is of value in the same classes of affections as inorganic ar-

senic preparations, and appears to be most suitable for cases where a constant, prolonged arsenical action is required.

In **anemias**, especially of the **pernicious** type, it has given good results in the hands of a number of observers. In **simple anemias**, it has shown evidence of its power greatly and, as a rule, rapidly to increase the hemoglobin percentage as well as in many instances the number of red cells. Administration by hypodermic or intramuscular injection is the procedure of choice; Dawes finds that the drug does not cause discomfort at the site of injection unless given in very large doses, such as $4\frac{1}{2}$ to 9 grains (0.3 to 0.6 Gm.). The method employed by this author is to have the pharmacist weigh out various doses— $1\frac{1}{2}$, $2\frac{1}{4}$, 3, and $4\frac{1}{2}$ grains (0.1, 0.15, 0.2, and 0.3 Gm.)—and place them in sterile $\frac{1}{2}$ -dram (2 Gm.) phials, tightly corked in order to prevent absorption of water from the air. At the time of injection the dry salt is placed in the barrel of the syringe, which has been previously sterilized. Boiling water is then drawn into the syringe until all the salt is dissolved. When the solution is cooled to about body temperature, the needle is quickly plunged deeply into the gluteal muscles—the skin having been suitably disinfected—and the solution slowly injected. The initial dose employed by Dawes is $\frac{1}{64}$ grain (0.001 Gm.) for each pound of body weight; later the total dose is gradually increased to 3 grains (0.2 Gm.) and frequently to $4\frac{1}{2}$ grains (0.3 Gm.).

In giving small doses and leaving intervals of non-treatment for fear of toxic results, one errs on the side of prudence. In most cases satisfactory

results are obtained only by using relatively large doses daily without intermission, and often for several weeks, especially in anemias of long standing. Of 14 cases of **pernicious anemia** treated with sodium cacodylate which had been reported to the author, 4 had short periods of improvement, alternating with exacerbation of the symptoms, and finally died. Of the remaining 10, reported as cured, 5 had been but so recently discharged (three, five, six, eight, and nine months) that they could not be claimed as cures, though every evidence of recovery was present. The other 5, however, seemed to be properly classed as well, for they had shown no recurrence of the symptoms for respectively fifteen months, eighteen months, twenty-two months, twenty-five months, and thirty-seven months. In these 5 cases careful blood-counts were made at frequent intervals, and the author had no doubt as to the correctness of the diagnosis. The author has records of 410 cases of anemia treated by himself and others, and in every uncomplicated one there was complete recovery. He has yet to see a case of anemia in which this drug has not rapidly increased the hemoglobin percentage and, as a rule, also the red cells. The most brilliant results have been in neuroses accompanying anemia. One patient with **tic douloureux** recovered, another improved; 15 out of 17 cases of **eczema** were cured; 22 patients with **psoriasis** gave only 9 recoveries and several seemed to be aggravated. **Neuralgias** and **gastralgias** generally responded favorably. It is important to have a perfectly pure salt. It would appear that sodium cacodylate is useful where arsenic is, and is less toxic in large doses. S. L. Dawes (Monthly Cyclo. and Med. Bull., June, 1911):

In pulmonary and other forms of **tuberculosis**, as well as in cachexias from various causes, including **malaria**, sodium cacodylate may be given with advantage to enhance gen-

eral nutrition and in particular to improve the condition of the blood. Dawes found that cases of **malaria** such as are seen in former residents of tropical and semitropical regions, and which had proven refractory to the persistent use of quinine, responded very promptly and permanently to the cacodylate. Malarial **gastralgia** has been found to be favorably influenced. According to Ewart, the cacodylate has a decided influence upon the hectic fever in phthisis.

Twenty-one cases were treated with sodium cacodylate, and, of these, 9 were selected as showing definite results: 4 cases of **pulmonary tuberculosis**, 2 cases of **skin diseases**, and 3 of **severe anemia**—2 of malarial and 1 of rheumatic origin. The drug was administered over long periods, preferably by hypodermic injection. As much as 1 grain (0.065 Gm.) daily may be given for days and even weeks. None of the usual toxic effects of arsenic were observed. In some cases a garlicky odor of the breath made its appearance. For hypodermic use the following formula was found satisfactory: Cacodylic acid, 1 dram (4 Gm.); caustic soda or sodium carbonate, a sufficient quantity to saturate; distilled water, enough to make 3 ounces (90 Gm.). This can be sterilized and will then remain perfectly neutral. E. M. Dupaquier (N. O. Med. and Surg. Jour., vol. liv, No. 2, 1901).

Other conditions sometimes benefited by arsenic medication in which sodium cacodylate has been tried and proven its worth include **neuralgias**, **tic douloureux**, **dysmenorrhea**, **bronchial asthma**, **Graves's disease**, **diabetes**, **leukemias**, **chronic rheumatic conditions**, and **chorea**. Dawes states that of 22 cases of **neuritis** treated with the drug 16 recovered. According to the same author, sodium caco-

dylate has proven much more satisfactory in the treatment of **chronic rheumatism** than other forms of arsenic. One case of **rheumatoid arthritis** was apparently checked by its use.

Sodium cacodylate has been employed with benefit in a vast variety of diseases: **grave anemia**, **cachexia** of varying origin, **tuberculosis** in its numerous forms,—**pulmonary**, **osseous**, and **visceral**,—**scrofulosis**, **herpetism**, **asthma**, cutaneous diseases of many types, **malaria**, disturbances of **menstruation**, **obesity**, **chorea**, **paralysis agitans**, **neurasthenia**, **myxedema**, **scleroderma**, **exophthalmic goiter**, **syphilis**, and **sarcoma**. It is best given by the hypodermic method. Patients can bear $\frac{5}{8}$ to $1\frac{1}{8}$ grains (0.054 to 0.108 Gm.) a day and continue such doses for at least two or three years without symptoms of arsenical poisoning or the occurrence of anatomical lesions in the viscera. The drug may also be administered by mouth, but it seems to be less well borne. This is probably due to processes of oxidation and transformation of the cacodylates into more active forms of arsenic. Armand Gautier (*Bull. de l'Acad. de Méd.*, vol. lxy, p. 20, 1901).

Various chronic skin diseases, such as **psoriasis**, **eczema**, **lichen ruber**, and **acne**, have proven amenable to cacodylate therapy.

Cacodylic acid considered by author the most powerful form of arsenic for **skin diseases**, being superior to Fowler's solution or other preparations of arsenic commonly used. Cacodylate of sodium and cacodylate of iron used in the form of pills, or in a solution, about 0.1 Gm. ($1\frac{1}{2}$ grains) of the salt being commonly given during the day. He has employed the drug in 50 cases. In only 1 patient, a hysteric, was the drug badly borne by the stomach. The garlic-like odor of the breath spoken of by some writers commonly occurred in anemic

patients having digestive disorders. The ordinary toxic symptoms of arsenic, such as diarrhea and dryness of the throat, were not noted. Two women who were especially susceptible to the ordinary forms of arsenic were able to take 0.1 Gm. ($1\frac{1}{2}$ grains) of the cacodylate of sodium. E. Saalfeld (*Therap. Monats.*, June, 1901).

Results in 45 patients suffering from **lichen ruber**, **eczema**, **psoriasis**, **simple anemia**, **splenic anemia**, **pernicious anemia**, **Hodgkin's disease**, **chorea**, **malaria with gastralgia**, and various **neuroses** reported. Of these, 34 were either entirely cured or much benefited, 11 unimproved, and 2 apparently made worse. The most striking result was in a case of **lichen ruber** with anemia. This patient received $2\frac{1}{4}$ grains (0.178 Gm.) of sodium cacodylate daily for six days, when the dose was doubled. Six days later the dose was increased to $6\frac{3}{4}$ grains (0.437 Gm.), and six days later to 9 grains (0.6 Gm.). This dosage was continued for thirty-four days, when it was reduced to $4\frac{1}{2}$ grains (0.3 Gm.). Four weeks later it was reduced to $2\frac{1}{4}$ grains (0.178 Gm.), and about a month later to $\frac{3}{4}$ grain (0.048 Gm.) every other day for three weeks, when it was omitted for ten days and then resumed for three weeks more every other day. A distinct cure followed. A sense of exhilaration was often experienced soon after the injection, and the treatment was almost always followed by a distinct gain in weight. The rapidity of improvement seemed to depend much upon the sufficiency of the dose. Dawes and Jackson (*Albany Med. Annals*, vol. xix, p. 139, 1908).

Rocaz, of Bordeaux, has recommended the use of sodium cacodylate in pediatric practice. He employed it in over 80 cases, in 60 of which the treatment was continued to its conclusion, and found that if given internally twice a day, in aqueous solu-

tion, with the meals, it is well borne by children and gives good results, notably in **anemia and incipient tuberculosis**. The condition of the kidneys should be examined into before beginning the treatment, and the susceptibility of the organism to the drug thereafter carefully watched. With these precautions, and by suspending the drug occasionally to guard against any tendency to cumulative action, Rocaz found it possible to avoid all disagreeable by-effects, observing neither any alliaceous odor of the breath, diarrhea, vomiting, nor skin eruptions.

The use of sodium cacodylate in **syphilis** has been suggested and more or less extensively tried. It has been argued, from the theoretical standpoint, that, since the cacodylate is less toxic and contains a slightly larger percentage of arsenic than Ehrlich's dioxydiamidoarsenobenzol, it should be comparable in its value in syphilis to the latter compound. While sodium cacodylate has in numerous instances proven very efficient in causing the initial lesion rapidly to heal and the secondary eruptions and mucous patches to disappear, recent experiences have not rendered it justifiable to regard the cacodylate as a substitute for dioxydiamidoarsenobenzol except, as Spivak states, in cases where the latter cannot be used, either for financial reasons or because of some physical condition of the patient.

Sodium cacodylate, given in doses of from 3 to 6 grains (0.2 to 0.4 Gm.), by mouth, and 1 to 2 grains (0.065 to 0.13 Gm.) in single doses daily hypodermically into the muscles, has a most striking effect on the syphilides, mucous patches, and primary chancre. From the latter the spirochetes dis-

appear * completely in forty-eight hours, the induration is markedly reduced in twenty-four, and it becomes a soft, clean ulcer in seventy-two hours. The primary dose should be from 2 to 4 grains (0.13 to 0.26 Gm.), according to the size and strength of the patient, and the drug should not be repeated within three or four days unless there are special indications for it. J. B. Murphy (Jour. Amer. Med. Assoc., Sept. 24, 1910).

Experiments reported which showed that sodium cacodylate has no spirillocidal action on infected rabbits in doses short of seriously injuring or killing the animals. Of course, facts gained by experiments on animals cannot be transferred directly to human medicine, but much of our knowledge of salvarsan has been obtained in that way. The therapeutic effect of sodium cacodylate is really due to decomposition and reduction products, such as cacodyl, arsenous and arsenic acids. The amount of reduction depends largely on personal idiosyncrasy, and this introduces an element of uncertainty. While there is no indication from experimental evidence for the use of sodium cacodylate in **syphilis**, it does not interfere, as has been suspected, with the action of salvarsan used subsequently. H. J. Nichols (Jour. Amer. Med. Assoc., Feb. 18, 1911).

Patients tolerate sodium cacodylate well, and its toxic effect does not show till after very strenuous treatment. A. J. Caffrey (Jour. Amer. Med. Assoc., March 4, 1911).

Case of tertiary **syphilis** with malignant symptoms, including a rapidly progressive ulceration of the eyelid, in which, ordinary specific treatment failing to cause immediate improvement, the patient was put on daily injections of $\frac{3}{4}$ grain (0.486 Gm.) of sodium cacodylate. Within forty-eight hours there was marked betterment, the ulcer becoming smooth and healthy in appearance,

and within a week the lid had entirely healed with very little deformity. With the exception of two or three of the larger foci situated on subcutaneous bone surfaces near the skin and elbow, there was rapid cicatrization and healing of the lesions. At the end of one week the injections were discontinued for a week, at the end of which time the Wassermann test had become negative. The treatment was then resumed with 1½-grain (0.1 Gm.) doses daily for one week longer, after which the man received 3 injections weekly for several weeks more. No internal medication was given until the reaction became negative, when tonic doses of iron and strychnine were administered. No bad effects from the arsenic treatment were observed. L. W. Crigler (Jour. Amer. Med. Assoc., March 25, 1911).

Sodium cacodylate used in 43 cases, each patient receiving from 14 to 16 injections on successive days. A fresh solution containing 4 grains (0.25 Gm.) of the drug to the dram (4 c.c.) of distilled water was prepared daily. The injections were at first made subcutaneously, then intramuscularly. The conclusion was reached that sodium cacodylate is useful in **syphilis**. While its action is not as rapid as that of salvarsan, it accomplishes results not unlike those of salvarsan. Care being taken that the salt is pure, and making a solution of it fresh every day, it is non-poisonous, even in doses as high as 5 or 6 grains (0.32 or 0.39 Gm.) injected daily for three weeks or a month. The only untoward effects ever noticed were slight shooting pains in the muscles, particularly those of the shoulder, and occasionally a muscle-spasm. There is no reaction at the site of injection. The drug should be used for effect, beginning with 3 grains (0.2 Gm.) daily and increasing as results are noted. It is cumulative in action, improvement continuing for a week or so after cessation of the injections. The best results are seen in early syphilis.

The drug has a marvelous effect on the initial lesion and on the maculoroseolar eruptions. The action on the papular syphiloderm is somewhat slower, but in large doses is pronounced. On the adenopathies the drug has practically no effect, enlarged cervical, epitrochlear, and inguinal glands persisting in spite of massive doses. Mucous patches and condylomata, however, clear up rapidly without any other treatment. The drug has an excellent alternative effect and can be used for that alone. All patients, whether their lesions were benefited or not, spoke of a sense of well-being, of added strength, of a better appetite, and even of an increase in weight. On the rupia and tertiary lesions sodium cacodylate has practically no effect. Immediately after the patient has had his course of injections he should be placed on mercury; otherwise, the external manifestations will recur. It would even be well to alternate a course of mercurial treatment with a course of cacodylate injections. The effect of sodium cacodylate on the Wassermann reaction is practically *nil*, but the drug should prove a useful adjunct in the treatment of syphilis. L. J. Spivak (N. Y. Med. Jour., March 2, 1912).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

CACTUS GRANDIFLORUS.—

This drug is obtained from the fresh (green) stems and flowers of the *Cactus grandiflorus*, Linné (*Cereus grandiflorus*, Miller and De Candolle; night-blooming cereus), a fleshy shrub bearing flowers 8 to 12 inches in diameter, growing in tropical America, especially Mexico. The drug is not official. The preparations generally used include the fluidextract, dose 2 to 10 or even 30 minims (0.12, 0.6, to 2 c.c.), and the tincture, dose 5 to 30 minims (0.3 to 2 c.c.), four times daily. An extract of the drug has also been used, in pill form. The taste of the fluid preparations is not

unpleasant; von Zelenski suggests that they be given in a little water or wine.

PHYSIOLOGICAL ACTION.—Cactus has been claimed by many to be a heart tonic, or at least a modifier of cardiac action. It is said to increase the heart rate, strengthen the cardiac contractions, and augment the volume of the pulse; while some of the older experimenters with the drug reported results substantiating these views, more recent experimental work has thrown considerable doubt upon the circulatory effects of cactus, at least in the normal individual. Hatcher and Bailey, in experiments upon cats, dogs, and frogs with samples of cactus obtained from Mexico, found the drug practically devoid of any tangible effect upon the circulation, whether administered by mouth or vein. When given intravenously, colossal doses of cactus exerted some slight action upon the heart, but the effect was so feeble that "its nature could not be determined." That the drug is thus practically inert when put to the test of modern pharmacodynamic procedures, shows conclusively that its action can in no wise be compared with that of the digitalis group of remedies, though the possibility of the production of some slight changes of heart-action in abnormal states is not necessarily precluded.

Cactus has been stated to act as a stimulant to the motor spinal centers, after the manner of strychnine. Recent experimental work seems to show, however, that this action, if present at all, is not very pronounced.

The drug is almost invariably well borne by the stomach and, so far as is known, has no cumulative effect.

THERAPEUTIC USES.—Cactus is said to be indicated especially in functional cardiac disorders such as nervous palpitation, in the irritable tobacco or coffee heart, the irregular heart-action which sometimes follows an attack of influenza, and the irregularity and precordial discomfort consequent upon gastric disturbance. It is claimed to act as a mild cardiac sedative and restore regularity of the heart rhythm where this is disturbed. Curtin believes it useful where cardiac irregularity "is associated with heart-strain or any other condition, in-

cluding dyspnea, hysteria, and hypochondriasis," as well as in all emotional irregularities, sometimes in Graves's disease, when the heart is weak, irregular, and rapid; in the aged who suffer from dyspnea, asthma, and a sensation of weakness in the organ (adding to the effectiveness of nitroglycerin in the cases), and in the weakened heart of the convalescent stage of exhausting diseases.

In organic heart disease, cactus is not claimed to compare in intensity of effect with digitalis and its congeners, though several authors, including Myers and Wilcox, have reported good results from its use in aortic insufficiency. In angina pectoris cactus has also been used with asserted benefit. According to Curtin, it is especially as an adjunct to heart tonics such as digitalis and strophanthus that cactus is useful. This author states that he has observed "a more tonic effect upon the heart from 3 minims of tincture of digitalis combined with fluidextract of cactus grandiflorus, 5 or 10 drops, and caffeine, $\frac{1}{4}$ to $\frac{1}{2}$ grain, than from a large dose of digitalis by itself." According to von Zelenski, cactus acts well in cardiac cases contraindicating digitalis, *e.g.*, in the presence of degeneration of the heart-muscle and in bradycardia caused by vagal irritation.

On the whole, it must be said that the experimental evidence now available is not suggestive of much power on the part of cactus as a heart tonic, and that the clinical evidence is not sufficiently unanimous and convincing to warrant much confidence in its action. S.

CADE, OIL OF (*oleum cadinum*), is a tarry oil derived from the wood of *Juniperus oxycedrus* by dry distillation. It is a thick, clear, brown liquid, with an odor of tar and a burning taste. It is but very slightly soluble in water, partially soluble in alcohol, and dissolves completely in ether, oils, and glycerin. Its constitution includes guaiacol and dioxybenzol combinations.

Oil of tar (*oleum picis liquidæ*) is frequently used as a substitute for oil of cade, as it has the same therapeutic qualities, is more easily obtained, and is used in the same class of cases.

MODE OF EMPLOYMENT.—Oil of cade is generally used in an ointment, or in admixture with an equal part of olive oil, in skin diseases of the dry, scaly variety, such as psoriasis. G. Gaucher has recommended the employment of the oil in association with acetone collodion as an excipient.

The remedy can thus be applied exclusively to affected points and kept in position; it does not stain linen, and the odor of the acetone to some extent disguises that of the oil.

Oil of cade is contraindicated in inflammatory skin conditions, or when weeping or exudation are present.

THERAPEUTIC USES.—While not adapted for use in acute eczemas because of its irritating qualities, oil of cade is a good remedy in **chronic eczema**, especially if itching is present.

In **psoriasis** the use of an ointment of oil of cade and salicylic acid after a bath will soften the scales and tend to improve the condition of the skin.

The following ointment is useful in any dry, scaly, itching skin condition without acute inflammation:—

℞ *Olei cadini* 3j (4 c.c.).
Acidi salicylici gr. x (0.6 Gm.).
Pasta zinci, Lassar.. 5j (30 Gm.).

M. et ft. unguentum.

Sig.: Rub well into the dry, scaly areas after a bath.

In **lichen planus** the following ointment will be found valuable, especially if itching is present:—

℞ *Phenolis* .. gr. x to xx (0.6 to 1.3 Gm.).
Olei cadini. m xxx to 3j (2 to 4 Gm.).
Pulveris amyli,
Pulveris zinci
oxidi .āā 3ij (8 Gm.).
Petrolati .. 3iv (16 Gm.).

M. et ft. unguentum.

Sig.: Apply locally as directed.

According to Carle, oil of cade is efficacious only in the simple, chronic form of lichen. It may be combined with simple plaster and wax, or with starch glycerite and tincture of quillaja, or with hydrated wool-fat, cocoa butter, lard or petrolatum. One of these combinations is forcibly rubbed into the lesions in the evening and kept in place overnight by a bandage; it is washed off the next morn-

ing with soap. Itching disappears at once under this treatment.

Oil of cade mixed with an equal amount of olive oil and rubbed into the scalp several times daily is an effective remedy in **tinea tonsurans**. W.

CAFFEINE. See COFFEE.

CAISSON DISEASE. See COMPRESSED AIR; DISORDERS DUE TO.

CAJUPUT OIL (*oleum cajuputi*) is a volatile oil distilled from the leaves and twigs of *Melaleuca leucadendron*, a tree of the family Myrtaceæ), native of the Molucca Islands. The oil is thin, greenish, or colorless, has a camphor-like odor and a slightly bitter taste, and is neutral in reaction. It is freely soluble in alcohol and has a specific gravity of 0.915 to 0.925. It is officially required to contain 55 per cent. of the chemically definite volatile oil *cincol* (eucalyptol).

MODE OF EMPLOYMENT.—Cajuput oil is used internally in doses of 2 to 10 minims (0.12 to 0.6 c.c.). Externally it is used in the form of a 10 or 20 per cent. liniment.

THERAPEUTIC USES.—In action oil of cajuput resembles the oils of turpentine and of eucalyptus, being a stimulant to mucous membranes in small doses, but an irritant in large ones. Internally, it is effective as a carminative and anthelmintic, and is also somewhat diaphoretic. It is useful in **ascariasis**, but is chiefly employed as a gastric intestinal stimulant in **flatulent colic**, and to prevent the griping of cathartics. In **serous diarrhea** it may be tried in 10- to 20- minim (0.6 to 1.3 c.c.) doses. The drug has also been used in **hysteria**, **dropsy**, **chronic rheumatism**, **bronchitis**, **scrofula**, and **syphilis**.

Externally, as a strong rubefacient, oil of cajuput is useful in **nervous headaches**, **chronic rheumatism**, and **chilblains**; as a stimulant to the cutaneous surface, in **psoriasis**, **pityriasis**, and **acne**; and as a parasiticide, in **tinea tonsurans** and **pediculosis**. W.

CALABAR BEAN. See PHY-SOSTIGMA.

CALCIUM.—Calcium is a metal belonging to the group of the alkaline earths, and having as its atomic weight 40.1. It is not found uncombined in nature, but occurs abundantly in carbonates, sulphates, and silicates, such as marble, limestone, chalk, gypsum, selenite, and other minerals, as well as in the tissues of plants and animals. The pure metal is a silvery white, hard, malleable, and ductile substance, which slowly decomposes water, but when heated unites readily with oxygen, with the production of a brilliant white light.

Calcium is used in medicine only in the form of salts, the physiological effects of which depend, in part at least, upon their acid constituent.

PREPARATIONS AND DOSES.

—The official preparations containing calcium are as follows:—

Calx (calcium oxide; lime; quicklime) [CaO]. Prepared from white marble or other native varieties of calcium carbonate, and occurs in hard, white or grayish-white masses. Calcium oxide is strongly hygroscopic; when left exposed to the air it absorbs both water and carbon dioxide, eventually becoming reduced to a powder. It is odorless, has a burning taste, dissolves in 760 parts of water at 25°C ., in about 1600 parts of boiling water, and is insoluble in alcohol. When to quicklime there is added about one-half its weight of water, heat is evolved, the two compounds uniting chemically with the production of calcium hydroxide (slaked lime) [$\text{Ca}(\text{OH})_2$]; upon further addition of water a suspension of the hydroxide is formed which is known as milk of lime, or whitewash. Calcium oxide is used in medicine chiefly in the form of lime water and carron oil.

Liquor calcis (lime water; “aqua calcis”). This is a saturated solution (0.14 to 0.17 per cent.) of calcium hydroxide in water. It occurs as a clear liquid with a strongly alkaline reaction and a feebly alkaline taste. When heated, some of the contained calcium hydroxide appears as a turbidity, which, however, disappears again if the liquid is allowed to cool. Unless kept over an excess of calcium oxide, lime water gradually loses its strength through absorption of carbon dioxide from the air, which results in the formation of a precipitate of calcium carbonate. The official dose of lime water is 4 fluidrams (16 c.c.). [The *syrupus calcis* (saccharated lime solution), no longer official, is a clear, yellowish fluid, containing a much higher percentage of calcium than ordinary lime water. It was intended chiefly as an antidote for oxalic acid, a precipitate of calcium oxalate being formed, which, however, is soluble in hydrochloric acid. The dose is $\frac{1}{2}$ to 2 drams (2 to 8 c.c.)].

Linimentum calcis (carron oil). Prepared by mixing equal volumes of lime water and linseed oil (*oleum lini*). Cottonseed oil might also be used. The resultant is a calcium soap of the oils employed, which is used externally as a dressing for burns.

Calx chlorinata (chlorinated lime; “chloride” of lime; “calcium hypochlorite;” bleaching powder), produced by the action of chlorine gas upon slaked lime, occurs as a white or grayish granular powder, having chlorine-like odor and a disagreeable saline taste. It dissolves only partially in water or alcohol, and colors litmus first blue, then white, owing to its bleaching property. Chlorinated lime gradually absorbs water and

decomposes on exposure to the air. It is officially required to yield at least 30 per cent. of chlorine gas. When added to water, it is changed to calcium hypochlorite [$\text{Ca}(\text{ClO})_2$] and calcium chloride; from the resulting solution, left exposed to the air, chlorine is evolved, a process which may be greatly hastened, in conjunction with the liberation of nascent oxygen, by adding dilute hydrochloric acid to the solution or by dissolving the dry chlorinated lime in dilute acetic acid. Calx chlorinata is used externally and in the sick-room, cess-pools, etc., as a disinfectant. It is not employed internally.

Calci sulphidum crudum, formerly *calx sulphurata* U. S. P., VIII (sulphurated lime; "calcium sulphide;" crude calcium sulphide; liver of lime) is a mixture of calcium sulphide [CaS] (60 per cent. at least) with unchanged calcium sulphate and carbon in varying proportions. It appears as a grayish powder with an unpleasant odor and taste, which is very slightly soluble in cold water and insoluble in alcohol, but dissolves more readily in boiling water, with partial decomposition. Exposed to moist air, sulphurated lime gradually breaks down with liberation of hydrogen sulphide. The internal dose is $\frac{1}{10}$ to 3 grains (0.006 to 0.2 Gm.); the substance is also occasionally used externally.

Calci bromidum (calcium bromide) [CaBr_2]. A white, granular, odorless salt, having a sharp saline taste, very deliquescent, soluble in 0.5 part of water and in 1 part of alcohol at ordinary temperatures. Dose, 10 to 30 grains (0.65 to 2 Gm.).

Calci carbonas precipitatus (precipitated calcium carbonate; precipitated chalk) [CaCO_3]. A fine, white,

amorphous, odorless, and tasteless powder, practically insoluble in water, insoluble in alcohol, and soluble in dilute acids with effervescence. Its solubility is increased by carbon dioxide and ammonium salts. Dose, 5 to 40 grains (0.3 to 2.6 Gm.).

Creta preparata (prepared chalk; drop chalk) consists of natural chalk—calcium carbonate—from which mineral impurities have been largely removed by suspension in water, the coarser materials present settling first and being discarded. It occurs as a white, tasteless powder, having the same solubilities as the precipitated calcium carbonate. Dose, 5 to 40 grains (0.3 to 2.6 Gm.).

Pulvis cretæ compositus (compound chalk powder). A mixture of 3 parts of prepared chalk with 2 parts of powdered acacia and 5 of powdered sugar. Used for the preparation of the next compound. Dose, 30 grains (2 Gm.).

Mistura cretæ (chalk mixture). Made by adding to 1 part of compound chalk powder and 2 parts of cinnamon water enough water to make 5 parts of the mixture. Dose, 4 fluidrams (16 c.c.).

Calci chloridum (calcium chloride) [CaCl_2], made anhydrous by fusion at the lowest possible temperature, occurs in white, hard fragments, which are odorless, but impart a very sharp saline taste. It is soluble in 1.3 to 1.5 parts of cold water, more freely in boiling water, in 8 parts of cold alcohol and 1.5 parts of boiling alcohol. It has an exceedingly great affinity for water, and deliquesces rapidly in the air. The pure chloride gives no residue when dissolved in water, and the solution is neutral to litmus. Dose, 5 to 30 grains (0.3 to

2 Gm.); average, $7\frac{1}{2}$ grains (0.5 Gm.),—always well diluted.

Calcii glycerophosphas (calcium glycerophosphate) $[\text{C}_3\text{H}_5(\text{OH})_2\text{PO}_4\text{Ca}]$ occurs as a fine, white powder, odorless, almost tasteless, and somewhat hygroscopic. It is soluble in about 50 parts of water at 25°C ., less soluble at higher temperatures; a saturated solution heated to boiling yields white, iridescent scales of it. Its solubility is increased by citric acid. It is insoluble in alcohol. A saturated aqueous solution of it is alkaline to litmus and to phenolphthalein. Dose, 3 to 15 grains (0.2 to 1 Gm.); average, 4 grains (0.25 Gm.).

Calcii hypophosphis (calcium hypophosphite) $[\text{Ca}(\text{PO}.\text{OH})_2 \text{ or } \text{Ca}(\text{H}_2\text{PO}_2)_2]$ occurs in the form of colorless or grayish, prismatic or scaly crystals, or as a white crystalline powder. It is odorless, but has a disagreeable, bitter taste; dissolves in 6.5 parts of water, and is insoluble in alcohol. Above 300°C . calcium hypophosphite decomposes, giving off inflammable gases. Dose, 5 to 30 grains (0.3 to 2 Gm.); average, $7\frac{1}{2}$ grains (0.5 Gm.).

Syrupus hypophosphitum (syrup of hypophosphites). Contains 4.5 per cent. of calcium hypophosphite and 1.5 per cent. each of potassium and sodium hypophosphites. Dose, 2½ fluidrams (10 c.c.).

Calcii lactas (calcium lactate) $[\text{Ca}(\text{C}_3\text{H}_5\text{O}_3)_2 + 5\text{H}_2\text{O}]$ occurs in white, granular masses or powder, odorless, nearly tasteless, and somewhat efflorescent. At 120°C . it becomes anhydrous. It is soluble in 20 parts of water, almost insoluble in alcohol. Dose, 5 to 30 grains (0.3 to 2 Gm.); average, $7\frac{1}{2}$ grains (0.5 Gm.).

Syrupus calcii lactophosphatis (syrup

of calcium lactophosphate). Contains a double salt of calcium in solution, and is made from 25 parts of precipitated calcium carbonate, 60 parts of lactic acid, 36 parts of phosphoric acid, and 50 parts of orange-flower water, with sufficient syrup to make 1000 parts. Dose, 2 fluidrams (8 c.c.).

Among the unofficial preparations of calcium are the following:—

Syrupus hypophosphitum compositus (compound syrup of hypophosphites, N. F.). Contains 3.5 per cent. of calcium hypophosphite, 1.75 per cent. each of potassium and sodium hypophosphites, 0.225 per cent. each of ferric and manganese hypophosphites, 0.11 per cent. of quinine, 0.0115 per cent. of strychnine, 0.375 per cent. of sodium citrate, and 1.5 per cent. of dilute hypophosphorous acid. Dose, 2 fluidrams (8 c.c.).

Emulsum olci morrhue cum hypophosphitibus (emulsion of codliver oil with hypophosphites, N. F.). Contains 50 per cent. of codliver oil, 1 per cent. of calcium hypophosphite and 0.5 per cent. each of potassium and sodium hypophosphites. Dose, 2 fluidrams (8 c.c.).

Elixir calcii bromidi (N. F.), containing 8.3 per cent. of calcium bromide. Dose, 1 fluidram (4 c.c.).

Elixir calcii hypophosphitis (N. F.). Dose, 2 fluidrams (8 c.c.).

Elixir calcii lactophosphatis (N. F.). Dose, 2 fluidrams (8 c.c.).

Emulsum olci morrhue cum calcii phosphate (N. F.). Dose, 4 fluidrams (16 c.c.).

Liquor hypophosphitum (N. F.). To replace syrupus hypophosphitum, U. S. P., when sugar is to be avoided. Dose, 1 fluidram (4 c.c.).

Liquor hypophosphitum compositus (N. F.). Dose, 1 fluidram (4 c.c.).

Syrupus calcii hypophosphitis (N. F.). Dose, 1 fluidram (4 c.c.).

Syrupus calcii chlorhydrophosphatis (N. F.). Dose, 1 fluidram (4 c.c.).

Syrupus calcii iodidi (N. F.), containing 8.3 per cent. of calcium iodide. Dose, $\frac{1}{2}$ fluidram (2 c.c.).

Syrupus calcii lactophosphatis et ferri (N. F.). Dose, 1 fluidram (4 c.c.).

Unguentum sulphuris compositum (N. F.) (Wilkinson's ointment; Hebra's itch ointment), consisting of precipitated calcium carbonate, 2 parts; sublimed sulphur and oil of cade, of each, 3 parts, and soft soap and lard, of each, 6 parts.

Calcii phosphas precipitatus (tricalcium phosphate) [$\text{Ca}_3(\text{PO}_4)_2$] (N. F. IV; Part II) is made from bone ash and occurs as a bulky, white, tasteless powder. Dose, 15 grains (1 Gm.).

Calcium carbide [CaC_2] occurs in grayish-black masses, which decompose with water, acetylene gas being evolved and a residue of slaked lime remaining. Used in gynecology as a caustic.

Dried calcium sulphate or gypsum (plaster of Paris) [$2\text{CaSO}_4 + \text{H}_2\text{O}$], a fine, white, tasteless powder, is no longer official. When $\frac{1}{2}$ its weight of water is added, a smooth paste is formed which rapidly hardens and expands.

PHYSIOLOGICAL ACTION.—

Lime salts form part of all animal tissues, particularly of the bones and teeth. They are also essential to the activity of certain ferments and glandular products, the thyroid secretion, for example. Under ordinary conditions the food supplies the body with enough of these salts to satisfy the needs of the tissues,—an excess being used during the process of growth,—

any surplus being eliminated mainly with the feces and urine.

An excess of calcium may be eliminated by the kidneys, but a simultaneous increased excretion through the bowel does not necessarily occur. A considerable quantity of the excess of calcium introduced may be retained for some time in the body. The increased excretion of calcium is accompanied by a rise in the urinary output of magnesium. The injections of calcium chloride (with sodium chloride solution) are followed by diuresis. It is suggested that the injection of either calcium or magnesium brings about the presence of an increased amount of either metal in the blood as an anti-toxic compensatory response of the organism whereby the toxic action of the injected metal is, to some extent, overcome. Mendel and Benedict (Amer. Jour. of Physiol., Sept., 1909).

It would appear under these conditions that in such diseases as osteomalacia, rickets, etc., which are due to deficiency of lime in the bones, the replacement of calcium salts would be indicated, but their use fails, mainly because deficient power to take up calcium underlies these disorders. What therapeutic value lime salts may have, therefore, is not related to their main physiological rôle in the body as components of osseous tissue in relation to quantity, but in their relation to metabolism.

Lime salts are not only necessary for the construction of the body and its growth, but also for keeping it healthy and in repair, and for the reproduction of the species. These salts become apparently pathological when, like inflammation, they endeavor to rescue diseased structures and to repair them. The selective and retentive power of the cell for calcium salts is probably in part under the influence of the calcium regulating factors. There is no such thing as calcareous degeneration.

The thing which does happen is a calcification—the result of a reparative process—in diseased structures. Calcium salts play a large part in the health of the individual, even while circulating in the blood. The lime salts are largely concerned in the contraction of involuntary muscle throughout the body. Bell and Hick (Brit. Med. Jour., Feb. 27, 1909).

The Indians of Mexico keep their teeth to an advanced age but develop caries when they become civilized and change their dietetic habits. The early wearing out of teeth the writer explains by the fine bolting of the flour which deprives it of the phosphates, etc., in the outer part of the grain. They are needed to keep the teeth strong. Especially during pregnancy, this lack of the earthy phosphates required by the mother and fetus may result in the woman's losing some of her teeth. He advises addition of earthy phosphates to the food during both pregnancy and lactation. Calcium phosphate seems indicated here. Bulman (Gaceta de la Acad. de Med., Mexico, Jan.-June, 1917).

Administration of a base or acid produced no significant effect on the balance of nitrogen, calcium, magnesium, and phosphorus in the dog. Administration of hydrochloric acid increased the urinary excretion of calcium and thereby altered the relation of calcium to magnesium in the urine. The calcium contained in milk was more effective than soluble calcium lactate in producing calcium retention. Givens and Mendel (Jour. Biol. Chem., Aug., 1917).

In their relations to the soft tissues, small doses of soluble calcium salts have been found to increase the energy of the exposed heart, and it is believed that calcium is essential to the dynamism of this organ. Small doses do increase the contractile energy of the myocardium, while large doses increase the rate of its contractions, cardiac paralysis en-

suing if the doses are sufficiently large. This action is of central origin, since the peripheral endings preserve their excitability. The skeletal musculature and the nerves are also stimulated by small doses of calcium and depressed by toxic doses.

The actual rôle fulfilled by calcium in all tissues is still to be determined.

The exact transformation which calcium undergoes in the body and the exact way in which it is utilized are unknown. We know, however, that a human being needs 1.5 Gm. (24 grains) of calcium per day in the first six months of life and from 0.9 to 1.1 Gm. (14 to 17 grains) after the fifth year. In the adult, calcium is absorbed chiefly in milk and its derivatives, and also in vegetables, meat, and water. Not all of the calcium, however, is absorbed and assimilated. The chlorides and the fluorides are less soluble than the bicarbonates and carbonates. The amount of calcium may be determined chemically in the various tissues. One of the most important effects of calcium is its stimulating action upon the heart and blood-vessels. Loeper and Boveri (Presse médicale, June 26, 1907).

Calcium salts have been used extensively to arrest hemorrhage on the plea that they increased the coagulability of the blood. This view has been challenged recently, but on inadequate grounds, *in vitro* experiments being totally misleading. The occurrence of thrombosis among the untoward effects of calcium intoxication sufficiently indicates the imprudence of casting aside the coagulation theory.

The effect of calcium salts on the blood is not so simple as some of our therapeutists have declared. Prof. B. J. Collingwood has lately been experimenting on the influence of these salts on the blood *in vitro*, and has told the Dublin Academy that the

rate at which the blood is shed makes a great difference in the time required for coagulation. None of his experiments gave any evidence that the addition of calcium increased the coagulability. In fact, an amount sufficient to appreciably increase the calcium content of the blood rather diminished the coagulability. From this it would seem that the therapeutical value attributed to these salts depends on other factors than the amount of calcium in the blood. The experiments were carried out at Sir A. Wright's laboratory at St. Mary's Hospital. In a number of trials on himself Professor Collingwood had not found that he could absorb any calcium. He thought that the clinical results reported might depend on vasoconstriction, and that injection of serum would be a more rational treatment for the prevention of hemorrhages, but serum differed much according to the time which had elapsed after withdrawal. London Letter (Med. Record, March 26, 1910).

Intramuscular injections of sodium oxalate into rabbits in doses of 0.18 and 0.2 Gm. ($2\frac{3}{4}$ to 3 grains) proved invariably fatal. The symptoms consisted in excitation and tonic and clonic convulsions. When calcium chloride solution was given in sufficient amount 1 minute after the oxalate injection, the animals survived. Gates (Jour. Exper. Med., Sept., 1918).

CALCIUM POISONING.—The toxic phenomena as represented in experimental animals are spasms indicating the predilection of calcium for muscular elements, with special manifestations in the direction of the heart: Arrhythmia, intermittent pulse, gradual diminution of cardiac power, and finally paralysis of the organ. In man, however, large therapeutic doses may produce venous thrombosis, numbness and tingling of the extremities, tinnitus, and deafness.

Having under his care a married woman aged 40 years suffering from a leg ulcer which seemed to be due to deep varicosity of veins, the writer gave her 15 grains (1 Gm.) of calcium chloride three times a day. At the time he did not further examine her, as she was fully dressed. On the third day of treatment the author was called to see her. She was complaining of numbness of the right side of the body and was cyanotic. The next day she was a little better, but still had the feeling of "pins and needles" in her right arm and leg. On the following day she had complete hemiplegia. There is no doubt on account of the slow onset that the lesion was due to cerebral thrombosis. Examination showed that the patient had a mitral lesion, and the author came to the conclusion that the calcium salts had something to do with the condition. Joseph Stark (Lancet, June 22, 1907).

Any untoward effect of calcium salts when taken in excess is counteracted, according to Sir James Barr, by citric acid 30 grains (2 Gm.) three times a day, which favors its elimination from the blood.

THERAPEUTICS.—*Sodium Lactate.*—Of all the calcium salts, this is the least irritating, the most rapidly absorbed and oxidized, freeing the base, and also the most agreeable to the taste.

Calcium given in the form of the lactate enters into the general metabolism or allows the calcium already present in the body to be utilized without loss. Given by the mouth there is no toxic effect from the administration of 20 Gm. (5 drams) of calcium lactate over a period of fifteen days. Towles (Amer. Jour. Med. Sci., July, 1910).

We have seen that calcium is not given to supply a deficiency of lime in the body in osseous diseases such as **osteomalacia** and **rachitis**, because

these disorders are due to its defective assimilation by the bone. But there is reason to believe that *thyroid gland* favors calcium metabolism and that its simultaneous use will cause calcium to prove useful in these disorders. Calcium lactate 10 grains (0.6 Gm.) and thyroid gland 1 grain (0.065 Gm.), given in a capsule after each meal, might be tried.

Calcium salts are useful in **cardiac weakness**, but, as emphasized by Sir James Barr (1909), they are contraindicated in mitral stenosis. They are contraindicated also when calcification of the arteries, especially the aorta, is probable, as in the aged. Drunkards and persons suffering from lead poisoning are also said to be unfavorably influenced by any preparation of calcium.

Calcium lactate has proven effective in **tetany**, especially the form due to surgical removal of the parathyroid glands. It may be given subcutaneously in 30-grain (2 Gm.) doses in saline solution, and the effect sustained by giving orally 10-grain (0.65 Gm.) doses in milk every four hours. Urgent cases have been controlled by an intravenous injection of a 5 per cent. solution, but it entails the danger of causing thrombosis.

In **latent gastric tetany** there are noted paresthesia in the hands and feet, over-excitability of certain nerves, fragile and ridged finger nails; short, stubby, thin hair, and rudimentary, small, irregular, furrowed teeth. Among the author's cases of acute and latent or gastric tetany, a number were greatly improved and relieved of nervous symptoms by administration of calcium in adequate doses. A. G. Brown, Jr. (Va. Med. Mthly, July, 1918).

The calcium lactate has also been recommended in the treatment of

epilepsy. In 15-grain (1 Gm.) doses, three times a day, it may either be used to alternate with the bromides or in their stead where these depressing salts, as is often the case, are contraindicated. It has also apparently proved effective in **puerperal eclampsia** to counteract convulsions.

The phenomenon of menstruation bears a close relationship to the calcium content of the blood. Menstrual discharge is found to be very richly charged with calcium, and this excretion coincides with a marked fall in the calcium content of the blood. Further, when a woman becomes pregnant such excretion of calcium necessarily stops and the question arises, How is it employed in the pregnant state? The needs of the embryo in the earlier months will be but small, so that for a few months the mother's calcium content must continue high. In the later months, however, the fetus will draw largely on the calcium salts in the mother's blood for the building up of the skeletal structures, and it is when this demand reaches its height, in the seventh month and after, that symptoms of the pre-eclamptic stage occur. **Eclampsia** and eclamptic symptoms, as well as the **albuminuria of pregnancy** which, in his opinion, may be due to paucity of calcium content of the blood, benefited by the administration of calcium salts in generous doses. Lactate of calcium was the form employed in doses of 15 grains (1 Gm.) every four hours until the symptoms abated, and then less frequently. A. C. F. Halford (Austral. Med. Gaz., Nov. 20, 1909).

Certain forms of **headache**, confined to the frontal region, with throbbing about the temples and occurring as a rule on awakening, ascribed by Luff to a "lymphatic" condition of the blood, are benefited by calcium. He administers 15 grains (1 Gm.) of the lactate one hour before meals.

There occurs often in women and less frequently in men a **headache** having the following characteristics:

(1) It is present and most severe on waking and tends to lessen or to disappear in from one to six hours. (2) It is usually a dull, heavy ache or a frontal or temporal throbbing; less often it is vertical, occipital, or unilateral; rarely it is neuralgic. (3) It is chronic and intractable, but may exhibit itself as the common occasional headache to which many are subject. (4) It is associated with a deficient coagulability of the blood. The subjects of this form of headache are usually of the lymphatic type. The expression is heavy and listless, the face is full and the eyes puffy, anemia is often present, and the whole bearing indicates mental and physical lassitude. Symptoms which are often associated with the headache are pain after eating, constipation, edema of face or extremities, dyspnea, chilblain or urticaria, and neuralgia. As treatment the author has employed the following in a number of cases with success: A calcium salt has been given in order to increase the coagulability of the blood; the lactate is to be preferred and may be administered in a mixture containing 15 grains (1 Gm.) of this drug, $\frac{1}{2}$ minim (0.03 c.c.) of tincture of capsicum, and 1 ounce (30 c.c.) of chloroform water, to be taken three times a day before meals. If the lactate cannot be obtained, the chloride may be substituted, 15 grains (1 Gm.) in 1 ounce (30 c.c.) of camphor water. Calcium lactate may be combined with bitters and with iron and strychnine, but not with alkalis or alkaline carbonates. G. W. Ross (Lancet, Jan. 20, 1906)."

The subjects of this form of **headache** are usually of the lymphatic type, with a tendency to slight edema of the face, eyelids, hands, and feet. There is generally some anemia and a varying amount of lassitude, both physical and mental. Calcium salts are practically specific in this disorder. The writer employs calcium

lactate, which has scarcely any taste, and is practically devoid of irritant properties. It should be fresh, as it decomposes after long keeping, when, instead of forming a clear solution in water, it forms a turbid one. The formula recommended by Dr. Ross (see above) is the one preferred. It should be continued for about six weeks. Constipation is a common accompaniment of the administration of the calcium salt, and should be controlled, preferably by an infusion of senna. Salines should not be given, as they precipitate the calcium salts. Of 45 patients with headache, 37, or 82 per cent., were cured, and 4 were benefited.

The same agent was used in other disorders. Seventy-eight per cent. of the patients with **chilblains** were cured. In 8 cases of **boils** associated with cold hands and feet, recovery followed the use of calcium lactate. Five patients with **aneurism** of the arch of the aorta were treated in the same manner, with considerable benefit in every case. The drug appeared to encourage the deposition of fibrin within the aneurismal sac. Very marked benefit also resulted in 3 cases of **hemoglobinuria**. Luff (Brit. Med. Jour., Jan. 30, 1909).

The lactate is also used in the treatment of **edema** of the lower extremities.

It is effective in **hemophilia** and **purpura** and the various forms of **hemorrhage**, viz., **hemoptysis**, a predilection to **epistaxis** when not due to mitral disease, **hematemesis**, and **intestinal hemorrhage**. Ringer cautioned against the too prolonged use of calcium in hemorrhagic disorders on the plea that otherwise opposite effects were produced. He advocated an intermission of a few days every three or four days. In **acute hemorrhage**, however, as much as 60 grains (4 Gm.) have been given at once to obtain prompt results.

The writer, following the suggestion of Wright and Paramore, has treated several cases of **hemophilia** and **purpura** with lactate of calcium, with markedly good results. As much as 60 grains (4 Gm.) were given in single doses, but the average dose is 15 or 20 grains (1.0 to 1.3 Gm.), three times a day. The most constant feature of the blood examinations, which were frequent, was the reduction in number of the blood-plates, which had been noticed also by others, but has hardly received due attention. Sudden reduction or disappearance of the blood-plates was observed in some instances to precede a hemorrhage, and the relationship between the small number of plates to the bleeding was very strongly suggested. This reduction also furnishes a valuable aid in the diagnosis of hemophilic hemorrhage, as in other forms of hemorrhage they are increased. A leucocytosis is also usually present in other forms, while it is uniformly absent in the anemia of purpuric hemorrhage. J. W. Coe (Jour. Amer. Med. Assoc., Oct. 6, 1906).

The writer has had extended experience in the use of calcium lactate to prevent **hemorrhage** and to control it in operations on the upper respiratory tract, especially in removal of tonsils and adenoids. Calcium lactate has a controlling influence in hastening coagulation of the blood. It is more effective in cases of **hemophilia** where coagulation is delayed than in normal cases. Before operations on tonsils and adenoids the personal and family history should be carefully inquired into, and in suspicious cases the coagulation period should be determined before operation. Such operations should not be undertaken in hemophilia cases, but when they are undertaken calcium lactate should be administered for a period before operation, and the same is advisable before all operations on the tonsils as a preventive measure. The drug should be continued after operation to diminish primary and

prevent secondary hemorrhage. Of all the calcium salts the lactate is the most effective, most agreeable to administer, and does not irritate the stomach. W. K. Simpson (Med. Record, Sept. 25, 1909).

Certain cutaneous disorders, especially those of a pruriginous type, are sometimes favorably influenced by calcium. **Urticaria**, **erythema**, **chilblains** with predilection to cold hands and feet, **boils**, and **offensive perspiration** often yield to the lactate.

The writer reports good results from the administration of a 5 per cent. solution of calcium lacticum without the addition of any corrigent, 1 or 2 tablespoonfuls before each meal for three or four weeks, in **purpura**, **urticaria**, **senile pruritus**, and **herpes gestationis**. Little or no benefit was obtained in angioneurotic edema, eczema, lichen ruber, habitual herpes, or pemphigus. Bettmann (Münch. med. Woch., June 22, 1909).

Calcium Chloride.—This salt is preferred by some for the treatment of **cardiac disorders**, referred to when the physiological action of calcium was reviewed, *i.e.*, those of an adynamic type. **Heart-failure** in infectious diseases in which this complication is apt to occur, such as **pneumonia**, **influenza**, **typhoid fever**, is efficiently counteracted with small doses frequently repeated.

The free use of calcium salts has a tonic action on the heart in cases in which there is a tendency to cardiac failure. The writer has given calcium chloride in doses of from 5 to 10 grains (0.3 to 0.6 Gm.) dissolved in water, every four hours, with most excellent results in cases of impending cardiac failure in **pneumonia**. The disagreeable saline taste of the salt is covered by 1 minim (0.06 c.c.) of the elixir of saccharin, containing $\frac{1}{20}$ grain (0.0032 Gm.) of saccharin, for each 10 grains (0.6 Gm.)

of calcium chloride. The mixture is given in water or milk and is said not to interfere with the use of other remedies. The salt has also proved efficacious in **cardiac disease** when the ventricular wall appeared to be losing power. In such cases the lactophosphate or glycerophosphate of calcium may be employed. Lauder Brunton (*Brit. Med. Jour.*, March 16, 1907).

The other indications of calcium chloride are similar to those of calcium lactate, but, its taste being extremely disagreeable, the lactate should always be given preference, even in cardiac disorders. Calcium chloride may prove useful to oppose **chloride retention**, but its action in this connection may be due to the breaking up of the salt and the elimination of the chlorine ion.

Calcium chloride is deemed by the writer a most useful drug, as is shown by the following indications for its employment: It was first used in the control of hemorrhage, **epistaxis**, **hemoptysis**, etc., and in **hemorrhoidal bleeding** and **hemophilia**. Here it acts by increasing the coagulability of the blood. On account of its influence in the production of fibrin-ferment it possesses a favorable effect in **urticaria** and **acute edema**; it is particularly useful in the urticaria resulting from the injection of therapeutic sera and in that due to intoxication. Its antihemolytic action renders it useful in **bilious hemoglobinuric fever**. In **nephritis** it sometimes reduced the albuminuria, the reduction being due to its antihemolytic action, to its antitoxic effect, and to its antagonism to the sodium ion, the latter being increased in renal lesions; also in small doses it is diuretic. Its effect in lessening nervous excitability gives it a field of usefulness in **tetany**, **glottic spasm**, **convulsions**, and **laryngismus stridulus**. As a **cardiac tonic** it increases the force of the heart and lowers arterial tension, and in **pneumonia**

it has a neutralizing effect upon the accumulation of the sodium salts in the organism. The drug is easily taken in doses of from 15 to 60 grains (1 to 4 Gm.) daily in milk, beer, or syrup of peppermint. It is important to interrupt its administration for one day in **every four**, and to suspend treatment every eight or ten days. In aged patients, who are liable to calcium retention, it should be avoided, for its administration may result in calcification of the vascular system. Carles (*Jour. de méd. de Bordeaux*, vol. xxxvii, p. 472, 1907).

Careful experimentation with rabbits and in human subjects showed that this salt is a valuable addition to the dechloridizing agents, and in cases of **chloride retention** should be prescribed in daily doses of $\frac{1}{2}$ to 2 Gm. ($7\frac{1}{2}$ to 30 grains). Bonnamour and Imbert (*Presse méd.*, Nov. 18, 1911).

Calcium chloride has been recommended to prevent antitoxin rashes, but the evidence available does not seem to warrant this practice.

To test the efficacy of calcium salts in the prevention of rashes following the administration of diphtheria antitoxin, the writer gave either the chloride or the lactate alternately in 62 consecutive cases, regardless of the severity of the disease or the size of the dose of antitoxin given, in 3- to 10-grain doses (0.2 to 0.65 Gm.), three times daily, omitting the third day. Of the 62 patients, 12 died too soon to be included in the observations; of the remaining 50, 27 received no calcium and 11 of these showed a rash the average duration of which was but three days; of the 23 who did have the calcium treatment there was a rash in 19 instances, with an average duration of more than eight days. This seems to indicate, the writer thinks, that the treatment is of little or no benefit if the results of the short series can be regarded as trustworthy. Cassidy (*Brit. Med. Jour.*, Dec. 16, 1911).

Calcium Hypophosphite.—This salt is thought by some observers to be one of the most readily assimilated of the series, particularly in **rachitis** and **osteomalacia**. It has been given with averred success in **pulmonary tuberculosis** to favor calcification of the tubercles and also in **neurasthenia** to enhance nerve nutrition. It is given in 5- to 10- grain (0.3 to 0.6 Gm.) doses three times a day, omitting the remedy a few days at short intervals.

Calcium Hydroxide Solution (Lime Water).—This valuable preparation is used mainly as a potent antidote in **arsenical poisoning**, and also in the treatment of **dysentery**, **infantile diarrhea**, owing to its antacid and mildly astringent properties. It is also employed to counteract **vomiting**; sips of a mixture of equal parts of lime water and milk will often arrest this symptom when other remedies fail. It is often added to the **milk** given to infants to prevent curdling and thus facilitate its digestion. Possessing as it does the property of dissolving mucus, it is used in **diphtheria**, **pseudomembranous croup**, **fibrinous bronchitis** to facilitate the elimination of the false membrane. It has been found efficient in **diabetes insipidus**.

Calcium Carbonate.—The reaction of this salt is similar to that of the above. It is often preferred because it may be prescribed in small bulk, powders for example, which may be added to water, milk, etc., to insure free dilution—a wise precaution to avoid irritation of the gastrointestinal mucous membrane.

Prepared Chalk or Chalk Mixture.—This preparation was formerly used extensively in the treatment of **infantile** and **choleraic diarrhea**, Mukherji

(1918), in bacteriologic experiments, found lime water, if used in sufficient amount, inimical to cholera vibrios.

LOCAL USES.—Several of the calcium preparations have been used locally to advantage.

Equal parts of lime water and olive oil form a thick fluid (*carron oil*) which is of great value in the treatment of recent **burns**. It affords a covering which protects the injury from the air and thus reduces the pain, while promoting resolution.

Lime water alone is also advantageous as a local application for pruriginous skin disorders in conjunction with the internal use of calcium lactate. Especially is this the case in **urticaria**, **erythema**, **chilblains**, and **offensive perspiration** of the axillæ and feet.

Calcium sulphate (*gypsum*) forms an efficient dusting powder for the eruption of **small-pox**. It reduces the tendency to ulceration, relieves the itching, and acts as a deodorant. The same properties render it useful in **leg ulcer**.

Chlorinated lime (*bleaching powder*) yields on exposure to the air hypochlorous acid. This in turn breaks up, yielding its chlorine. It is very active, therefore, as a disinfecting and deodorizing agent for cesspools and the excretions of invalids especially. A solution of 1 part to 100 parts of water destroys the pathogenic organisms of urine, fecal discharges, sputum, etc., and is preferred to other disinfectants owing to the fact that it does not injure bedding, clothing, etc., though of course bleaching these articles if their colors are not fast. Freely diluted it is also useful in the local treatment of **ulcers**.

One of the more recent uses of a

calcium salt is to replace the bismuth in Beck's paste in the treatment of **sinuses** and **deep ulcerations** and thus avoid its untoward effects (see Bismuth, this volume). Equal parts of calcium carbonate and petrolatum were found by Mitchell equally effective.

Crude calcium sulphide, besides its use as a depilatory, has been recommended internally in 1-grain doses in boils, suppurative processes generally and acute infectious diseases. Its efficiency is doubtful (Sollmann).

Calcium carbide has recently been advocated as a caustic for inoperable **cancer**.

The writer has used calcium carbide extensively as a caustic in the treatment of various superficial lesions, and prefers it to all other substances for this purpose. In contact with water, the carbide decomposes into calcium oxide (lime) and acetylene gas. The chief advantages he claims for it are that it does not attack healthy skin if the latter be kept dry, affecting only diseased areas which present a moist surface; that it causes but little pain; that it is strongly hemostatic and antiseptic, and that it is non-toxic. L. Desguin (Gaz. méd. belge, May 25, 1911).

Chlorinated lime has been extensively used for the **sterilization of drinking water** particularly by troops. This action has been attributed to the chlorine the salt contains.

The writer found that the active agent in sterilization of drinking water by means of chloride of lime is not the chlorine, as supposed, but the oxygen, the substance being a double salt ($\text{Ca}(\text{ClO})_2 + \text{CaCl}_2 + 4\text{H}_2\text{O}$), in which the oxygen is given off readily and absorbed by the water. A prolonged action is required to insure complete sterilization. If the contact of small amounts of chloride with the bacteria is short,

there is only a partial germicidal action and an inhibition of bacterial growth. The virulence of the bacteria, following incomplete sterilization, is not changed. Antonovsky (Roussky Vrach, Apr. 21, 1912).

In a study of the limitations of chloride of lime tablets for the sterilization of drinking water by troops, the writer ascertained that their efficiency depended not only on the kind of the germ, but also on its resistance to the action of germicides. The cholera spirilla are destroyed very readily. Some of the other micro-organisms require a much longer contact. In the presence of considerable organic matter in the water, a larger quantity of chlorine is required. Also, the amount of chlorine will be influenced by the reaction of the water. In the author's experiments, 2 milligrams ($\frac{1}{32}$ gr.) of chlorine to the liter (quart) of water killed the cholera spirilla in 10 minutes; the typhoid bacilli were destroyed in 2 hours and 40 minutes; the dysentery bacilli in 2 hours and 45 minutes; and the colon bacilli in 3 hours and 5 minutes. Archipiantz (Roussky Vrach, Apr. 30, 1916).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

CALOMEL. See MERCURY.

CALUMBA (or *colombo*) consists of the dried root of *Jateorhiza palmata* (natural order Menispermaceæ), a plant of the southeastern coast of Africa and of the East Indies. It has a slight odor and an aromatic, very bitter taste, and contains the alkaloid *berberine*, a bitter, neutral principle known as *columbin* ($\text{C}_{21}\text{H}_{22}\text{O}_7$), *columbic acid* ($\text{C}_{21}\text{H}_{22}\text{O}_8 + \text{H}_2\text{O}$), cholesterol and mucilage, but no tannin.

PREPARATIONS AND DOSE.—*Calumba* (calumba root). Dose, 30 grains (2 Gm.).

Tinctura calumbæ (tincture of calumba). Dose, 30 minims to 2 fluidrams (2 to 8 c.c.).

Fluidextractum calumbæ (fluidextract of calumba; N. F.). Dose, 15 to 60 minims (1 to 4 c.c.). No longer official in U. S. P.

The British Pharmacopœia recognizes also:—

Infusum calumbæ (infusion of calumba).
Dose, $\frac{1}{2}$ to 1 fluidounce (16 to 32 c.c.).

THERAPEUTIC USES.—Calumba is one of the best of the simple bitters, having no astringency, but on the other hand, through its bitter taste, stimulating the flow of saliva and gastric juice and promoting gastric circulation, thus increasing the appetite and improving digestion. Though it is one of the least irritating of the gastric tonics, its long-continued use may induce a catarrh of the stomach or diarrhea.

Calumba, with quassia and chirata, is peculiar among the bitter tonics in containing no tannic acid; it may therefore be prescribed in combination with iron without causing precipitation, as in the following:—

R. Fluidextracti calumbæ. f3iv (16 c.c.).

Tinctura ferri citro-
chloridi (N. F.).... *f3ij* (8 c.c.).

Elixiris aromatici,
q. s. ad *f3iij* (100 c.c.).

M. Sig.: One teaspoonful an hour after meals.

The drug is very useful in **atonic dyspepsia**, with discomfort after meals, and in the period of **convalescence** from acute diseases to promote appetite and digestion. Pouchet recommends the following preparation containing calumba as a bitter tonic:—

R. Extract of calumba,
Extract of quassia,
of each 2.5 Gm. (gr. xl).
Malaga (or Ma-
deira) wine 500.0 Gm. (Oj).

M. Sig.: One or two tablespoonfuls one-half hour before each of the two principal meals.

In **diarrhea**, **dysentery**, and **cholera morbus**, calumba has been found valuable by some. It may also be tried in the **vomiting of pregnancy** and in **seasickness**. In **pulmonary tuberculosis** calumba is useful to stimulate the appetite. Schulz used it successfully in the diarrhea of phthisis, administering the tincture in doses of 40 minims to 3 drams (2.5 to 11.25 Gm.) once or twice a day.

CALX. See CALCIUM.

CAMMIDGE'S REACTION.

See PANCREAS, DISEASES OF.

CAMP FEVER. See TYPHUS.

CAMPHOR.—Camphor is a tough, crystalline, white, translucent gum obtained mainly from the *Cinnamomum camphora* (Linné), or camphor laurel, indigenous in eastern and southeastern Asia. It is a dextrogyrate modification of the saturated ketone, $C_{15}H_{11}CO$, purified by sublimation. It evaporates gradually on exposure to the air at ordinary temperatures, and sublimes when moderately heated without leaving a residue. It should be kept in a cool place in well-stoppered bottles.

Camphor has a penetrating aromatic odor and a pungent, somewhat bitter taste, which leaves in the mouth a feeling of freshness or coolness. It is sparingly soluble in water, but readily so in alcohol, ether, chloroform, carbon disulphide, petroleum, benzine, and in fixed and volatile oils. It cannot be reduced to powder in its normal state, but is readily pulverizable when a little alcohol, ether, or chloroform is added to it.

PREPARATIONS AND DOSE.

—The official preparations of camphor and their doses are as follows:—

Camphor (camphor), 2 to 10 grains (0.12 to 0.6 Gm.). It should be given in the form of pills or in capsules.

Aqua camphoræ (camphor water), which contains 0.8 per cent. of camphor. Dose, $\frac{1}{2}$ to 2 fluidounces (15 to 30 c.c.).

Linimentum camphoræ (camphorated oil, or camphor liniment), composed of camphor, 20 parts, and cottonseed oil, 80 parts. For hypodermic and local use.

Linimentum saponis (soap liniment), composed of camphor, 4.5

parts; soap, 6 parts, and alcohol, 100 parts. For external use.

Spiritus camphoræ (spirit of camphor), composed of camphor, 10 parts; alcohol, 100 parts. Dose, 10 to 30 minims (0.65 to 2.0 Gm.).

Tinctura opii camphorata (camphorated tincture of opium, or paregoric), composed of camphor, powdered opium, benzoic acid, oil of anise, of each, 4 parts; glycerin, 40 parts; diluted alcohol, enough to make 1000 parts. Each fluidram (4 Gm.) contains $\frac{1}{4}$ grain (0.016 Gm.) powdered opium and $\frac{1}{4}$ grain (0.016 Gm.) of camphor. Dose, 1 to 4 fluidrams (4 to 15 c.c.).

Camphora monobromata (monobromated camphor), a substitution compound of camphor ($C_{10}H_{15}BrO$), prepared by heating camphor and bromine, dissolving in benzine, and crystallizing from hot alcohol. It occurs in the form of colorless scales or needles, having a camphor-like odor and taste. It differs from camphor, however, in not being volatile. Its solubilities are the same as those of camphor. Dose, 2 to 5 grains (0.12 to 0.3 Gm.)

No longer official is *camphoric acid*, a dibasic organic acid. $C_8H_{14}(COOH)_2$, obtained by the oxidation of camphor, occurs as colorless crystals, having a faint aromatic odor and a slight camphor-like taste. It is soluble in 125 parts of water and readily in alcohol and fatty oils. Dose, 10 to 30 grains (0.6 to 2 Gm.), administered preferably in capsules.

Besides the above preparations of camphor, there are several that are used to advantage. Several of these we owe to the fact that, when camphor is triturated in about molecular proportions with menthol, thymol, phe-

nol, and chloral hydrate, syrupy fluids termed *camphor-menthol*, *camphor-thymol*, *camphor-phenol*, and *camphor-chloral* are obtained, which are mainly employed locally.

PHYSIOLOGICAL ACTION.—

Camphor in small doses seems to exert a mildly sedative action on the nervous system, while large doses stimulate the latter, the cerebrum and medulla especially, causing psychic exultation, visions, delirium, hysterical paroxysms, and even epileptiform convulsions, suspending general sensibility. It also stimulates the heart and increases the *vis a tergo* motion of the blood, but this action becomes especially manifest when the cardiac action is depressed. Though stimulating the vasomotor center, it tends to dilate the peripheral blood-vessels. On the whole, however, the effects of camphor on the blood-pressure are variable.

Experiments by the writer showed that, when the blood-pressure of the animals experimented upon was reduced by means of chloral, camphor subsequently injected had no effect or else brought about a slight rise or fall.

Slight fluctuations are, however, common with chloral alone. Dilute solutions of camphor, allowed to circulate directly through the heart, will sometimes show a decided stimulating effect, but more frequently no influence could be observed. One action, however, is fairly constant; if the heart of a warm-blooded animal has ceased beating and simply flickers, camphor will almost invariably bring about a return of co-ordinated contractions. It is possible that this will explain the stimulating action of camphor in severe collapse, though the conditions are very different in the living body. E. Seligmann (Arch. f. exper. Path. u. Pharm., Bd. lii, Nu. 5, 1905).

Camphor exercises a favorable effect upon the heart muscle, when it is poisoned by chloral, muscarine, or strychnine, but the authors consider it unreliable as a cardiac stimulant. Heard and Brooks (*Amer. Jour. Med. Sci.*, Feb., 1913).

Broken compensation in valvular disease of the heart, with cardiac failure, is not suited to camphor, but while we may not be able to explain satisfactorily why it acts as a cardiac stimulant, the fact remains that such is the case when the drug is employed in the proper sort of cases. Hare (*Therap. Gaz.*, Apr., 1913).

The long continued administration of camphor to rabbits did not seem to impair in any way the functioning or the structure of the heart, but rather to increase its functional capacity. But it did not render the heart more resistant to phosphorus poisoning or to diphtheria toxin, and did not aid in throwing off the effect of ether. The writer found small doses of camphor very useful in keeping up the tone of the heart with chronic myocarditis. Sigerist (*Corresp. blatt. f. schweizer Aerzte*, Dec. 22, 1917).

Whether the effect be exerted upon the nervous system and through the circulatory variations it produces in the latter, the fact remains that camphor allays, in small therapeutic doses, both nervous excitement and muscular spasm, while promoting a general sensation of warmth. The secretions are not affected by the drug with the exception of the sweat, owing doubtless to the dilatation of the cutaneous blood-vessels. The temperature is not sensibly influenced unless fever be present, when it tends to lower it somewhat. While the respiratory function is enhanced by therapeutic doses, owing to their stimulating action on the respiratory center, toxic doses depress the latter. Its great volatility renders the action

of camphor in small doses ephemeral; it is advisable, therefore, to administer it preferably in small, but frequently repeated doses.

Local Action.—Locally applied, camphor causes slight irritation, a sensation of freshness due to its evaporation, and partial anesthesia. Taken orally in small doses it causes a feeling of warmth and in large doses marked irritation, but the gastric mucosa is particularly sensitive to its action and ulceration has been known to occur. Camphor is slightly antiseptic. When administered hypodermically it causes pain.

Absorption.—Camphor is absorbed with fair promptness, but irregularly, according to the oxidizing power of the fluids with which it comes into contact. It combines in part in the liver with glycuronic acid to form camphoglycuronic acid, a harmless combination, and is also partly exhaled through the lungs and eliminated by the skin, the excess remaining in the body, causing therapeutic or toxic phenomena according to the quantity taken.

Part of the camphor enters into a harmless combination with glycuronic acid in the body and part is exhaled through the lungs. The fraction remaining is what exerts the therapeutic action on the vascular system. From his research, the writer concludes that the fatal dose is about 1 Gm. (15 grains) to the pound of body weight of a healthy human being or animal. The toxic dose is a third less. These proportions are less in persons who at the moment of the injection are not able to form or have not already on hand the amount of glycuronic acid necessary to combine with the camphor to form the harmless camphoglycuronic compound. As glycuronic acid is a product of the oxidation of grape-

sugar, when there is a lack of either grape-sugar or of oxygen, there will be correspondingly less glycuronic acid, and in such case a smaller proportion of camphor will have a toxic action. This assumption was confirmed by his experiences with twenty out of thirty-five rabbits on which he experimented. Healthy rabbits bore intravenous injection of 0.08 Gm. ($1\frac{1}{4}$ grain) of camphor without apparent injury, but this amount proved rapidly fatal if they had been fasting, and thus deprived of grape-sugar, for from six to nine days previously. Similar experiments in which the animals were deprived of oxygen, instead of the grape-sugar, proved equally fatal when the camphor was injected, the animals succumbing after injection of 0.02 or 0.04 Gm. ($\frac{1}{3}$ or $\frac{2}{3}$ grain) of camphor, from one-fourth to one-half the previously tolerated dose. These findings were corroborated by the effect of glycuronic acid injected at the same time with the camphor. Animals thus injected showed little, if any, disturbances and were soon as lively as ever, while the controls all died. These experiences warn physicians to be cautious in administering camphor to patients whose carbohydrate metabolism is defective, such as cachectic persons or those in inanition, or in severe cases of diabetes or chloral poisoning. On the other hand, great caution is necessary in administering camphor to persons with a deficient supply of oxygen, as in carbon dioxide intoxication, in severe cardiac defects, in advanced bilateral pneumonia, in severe sepsis, and to eclamptics. In eclampsia (as in the case reported by the writer) and psychic excitement, camphor is further contraindicated on account of the fact that its base of action is in the central nervous system. K. Happich (Jour. Amer. Med. Assoc., from *Centralbl. f. Gynäk.*, Dec. 30, 1905).

POISONING.—Although the textbooks hardly refer to the fact, poison-

ing by camphor is by no means infrequent, even under the influence of comparatively small doses, the sensitiveness to its action varying considerably in different individuals, weak subjects being especially vulnerable. While 30 grains (2 Gm.) will cause threatening phenomena in the strong, 6 to 7 grains (0.4 to 0.5 Gm.) will suffice to do so in a weak or old adult.

The use of large doses of camphor as a bactericide and analeptic is a dangerous practice. Some surgeons have thrown as much as 50 or 100 c.c. (1.7 or 3.4 ounces) of camphor oil into the peritoneal cavity after a laparotomy, and the belief has been freely expressed that camphor can do no harm. Even years ago Ziemssen stated that this substance "has no maximum dose." Nevertheless camphor is quite toxic to small animals, to the amount of 1 cg.— $\frac{1}{10}$ grain (3 cg.— $\frac{1}{2}$ grain—will kill a rabbit). Given as vapor and respired by the animal, the toxicity is notably increased. The danger for mankind lies in giving large doses to a badly weakened subject. The overaction of camphor is expressed ordinarily by marked slowing of pulse and tendency to collapse. Happich (*Münch. med. Woch.*, March 19, 26, and April 2, 1912).

Case observed by the writer in which a baby of 18 months was given a brimming teaspoonful of camphorated oil by mistake, containing from 14 to 15 grains (0.91 to 1 Gm.) of camphor, without causing any symptoms of note. D. J. Milton Miller (*Jour. Amer. Med. Assoc.*, Aug. 15, 1914).

The writer describes 5 cases in which epileptiform seizures were caused. The camphor had been prescribed for gonorrheal urethritis but the patients took the doses too often. In the fifth patient the camphor had been prescribed to relieve a painful cystitis, 1.5 gram (23 gr.) in the course of 2 hours. The convulsion occurred the following morning.

There was only 1 seizure in each case, but all described it as resembling a typical epileptic seizure. The camphor had been given with hexamethylenamine in all. Austregesillo (*Semana Medica*, Mar. 4, 1915).

Death followed ingestion of 1 dram (4 Gm.) of camphorated oil by a baby 3 weeks old. The maximum temperature was 100.6° F. (38.1° C.) and the child only showed signs of bronchitis, which had been diagnosed before the camphorated oil was administered. After 43 hours the child died very suddenly in a cyanotic attack. Haas (*Amer. Jour. of Obstet.*, June, 1916).

A sensation of heaviness about the head, developing into a violent headache and vertigo in some cases; marked weakness, and a tendency to collapse initiate the toxic phenomena. Nausea and vomiting are often observed. A sensation of burning in the mouth, throat, and stomach, with eructations which give off an odor of camphor, are valuable diagnostic signs when they occur, but this is not always the case. The breath may also smell strongly of camphor. Delirium is a common symptom which may be observed when therapeutic doses as small as $\frac{3}{4}$ grain (0.05 Gm.) are administered in the course of infectious diseases.

Two cases in which marked delirium followed 9 and $9\frac{3}{4}$ doses. The effect on the hearts had been very satisfactory, but an intractable delirium had set in in both cases. At first this was not ascribed to the drug, which was continued. Bromine was given to quiet the condition, without success. After three days it occurred to the writer that the camphor might be responsible for the delirium; he therefore discontinued the powder and gave bromide alone. The untoward symptom disappeared promptly. F. Bohlen (*Deut. med. Woch.*, May 16, 1901).

The pulse, full and strong at first, gradually weakens and becomes more rapid until finally it is uncountable. The temperature follows a somewhat similar curve, hypothermia corresponding with an advanced stage of poisoning, attended also by coldness of the extremities, being usually present. Free sweating starts early, but may continue throughout the advanced stage. The face, flushed at first, becomes cyanosed; these phenomena are attended with more or less dyspnea and rapid or irregular and sometimes stertorous breathing. The pupils are moderately and equally dilated; but later the eyes may become staring, with loss of the conjunctival reflex.

Case of camphor poisoning in a Hindu married woman aged 28 who had an attack of choleraic diarrhea in the month of July. She had copious stools and vomiting. A bottle of Rubin's spirits of camphor was administered by someone in the house in three doses. The diarrhea was stopped, but the patient began to vomit, and experienced a terrible burning pain in the stomach and the throat.

The author saw the patient three days after the accident. The patient still complained of pain in the throat and stomach, and vomiting was still present. She was anemic and pale; conjunctiva was bloodless. There was complete anorexia and intense thirst. She was helpless, though quite restless, and had a low muttering delirium, a vague look, and was evidently in anguish.

There was fever at first, palpitations, and occasional symptoms of suffocation. The pulse was slow and feeble. The lungs were quite free. The bowels were constipated and the urine scanty. She was sleepless for some days.

She was given a bromide mixture with belladonna. She slept well, but

delirium was not abated at first. Excepting whey and barley water, no solid food was given for four or five days until the burning sensation in the throat and stomach passed away. On the fourth day the writer gave her a gastric sedative to allay the pain and irritation. She was now given milk and soup daily and gradually rallied. Roy (*Calcutta Med. Jour.*, Aug., 1911).

The nervous phenomena are, as a rule, very marked. The delirium referred to above may be preceded or followed by hysterical excitement, or it may be accompanied by a sensation of swinging or lifting in the air. In most cases, however, a period of excitement is followed by unconsciousness or epileptiform convulsions. The latter are often typical, being preceded by a loud outcry and accompanied by frothing at the mouth, biting of the tongue, involuntary urination, etc., the scene often ending in coma and death.

Case in a man who had taken a dose from a bottle which contained only camphor and alcohol. The patient was unable to stand. Respirations 60 to 70 per minute; pulse 130 and weak, but regular. Face bore an anxious expression and was very pale; lips cyanotic; pupils practically normal and equally dilated. Cold perspiration on forehead and face; extremities cold and trembling. Patient was thoroughly conscious, but was unable to speak above a whisper, and then but a few words and with much difficulty. There was no pain at all, at any time, but he complained of a tingling and numbness of the whole body, beginning in the toes and extending upward, and for the time being a paralysis of the legs. There was a feeling of swinging in the air and a sense of impending death from inability to breathe. It occurred to the writer that he might have a case either of wood alcohol or camphor poisoning, but on smelling

the bottle he decided it must be camphor.

Immediately $\frac{1}{250}$ grain (0.0002 Gm.) of **glonoin** was given by the mouth and $\frac{1}{30}$ grain (0.002 Gm.) of **strychnine nitrate** hypodermically. Within a very few minutes there was a cessation of difficult breathing, but it was soon followed by another wave-like attack which began in the feet, and swept up the limbs and arms to the back, and finally to the top of the head. Marked dyspnea accompanied each wave-like attack, which was increasing in frequency, duration, and severity until the glonoin and strychnine were given.

Shortly after giving the above, the writer gave a pint of warm water, to which a little salt had been added, to precipitate any camphor remaining in the stomach, and also to promote vomiting, the patient at this time being sufficiently recovered to object strenuously to the passage of the stomach-tube. The warm salt water produced free emesis. The vomited matter consisted of material resembling the precipitate formed by placing camphor in water and smelled strongly of camphor. Several pints of the **warm salt solution** were repeated and vomited until the stomach was apparently pretty well cleansed.

From this time on, the improvement was rapid, but there was slight dyspnea for a day or so, and from the continuance of a few doses of glonoin and strychnine no further attention was given. O. M. Rhodes (*Med. Fortnightly*, Aug. 25, 1906).

Case of poisoning by camphor liniment. An infant 1 year and 4 months old swallowed about half an ounce (15 Gm.) of the liniment. The *linimentum camphoræ* of the British Pharmacopœia contains camphor, in flowers, 1 part; olive oil, 4 parts; so that about 1 dram (4 Gm.) of solid camphor in solution was probably taken. Although the infant was promptly "turned over" and made to vomit, after an hour the symptoms began to develop. The eyes gradually became staring, she moaned,

and convulsions began. She was then given some salt and water, and vomiting occurred. When the writer saw her there were very marked convulsions, with irregular breathing, flushed face, and profuse perspiration; the pulse was rapid, the pupils were moderate and equal in size and inactive to light, and there was no conjunctival reflex. The breath did not smell of camphor, and the mouth was not sore. The infant was put in a hot bath, with cold cloths to the head. The stomach was washed out with warm water until quite clear of oil and *débris*, the washings being placed in four successive bowls. The first two contained food remains in small quantity, with a considerable amount of oil coating on the top, smelling distinctly of camphor. The last two showed the merest film of oil and did not smell. The pulse was about 200, temperature in rectum (taken twice) 106.4° F. (41.5° C.). Remedies seemed to have little or no effect. Chloral hydrate (3 grains—0.2 Gm.) by the rectum, small doses of potassium bromide by stomach-tube and by rectum, hot milk and water similarly given, and brandy were tried. Chloroform was given very cautiously, and with even the most sparing dosage the fits were to some extent controlled. But they became periodic, and in the intervals the breathing was so markedly stertorous, and the face more cyanosed than before, that the anesthetic was suspended. While giving chloroform the fits were heralded by a flickering of the eyelids, the spasms spreading to the abdominal and back muscles and then to the extremities. There was usually at first conjugate deviation of the eyes and drawing of the mouth to the left, followed by the turning of the eyes and mouth to the right. On ceasing the chloroform the convulsions became more continuous, but were not so violent; the breathing was decidedly better, and the face a more natural color. Later there was a slight return of conjunctival reflex. Soon collapse

set in, and the infant died. Barker (Brit. Med. Jour., April 16, 1910).

The urine is apt to be scanty and cloudy and may contain blood-corpuscles, red and white. No albumin is usually found.

No untoward effects usually follow recoveries, the exceptions being temporary paralysis, meningeal congestion, tingling and numbness, or soreness of the legs and abdomen.

Case of a lady 78 years of age who took an unknown quantity of spirit of camphor. About an hour after taking it she became comatose, and finally appeared to be dead. Consciousness returned after a considerable interval, and it was found on examination that her right hand and right side of her face were paralyzed. In four weeks she was able to walk about the room with assistance. Some five months later she could pick up a pin from the floor with the afflicted hand, and there was no perceptible trace of the facial paralysis. Treatment consisted of normal liquid of *nux vomica* and gentle massage to the affected parts. T. B. Greenley (Amer. Pract. and News, July 15, 1900).

Case of meningitis due to camphor poisoning in a child 2½ years of age who was found unconscious, covered with cold perspiration, and with an uncountable pulse. These symptoms were noted at two o'clock in the afternoon; at eight the same morning a teaspoonful of camphorated oil had been given in mistake for castor oil. Vomiting had been frequent. Potassium bromide was injected into the rectum. This controlled the convulsions. An improvement was gradual until the third day, when symptoms of meningitis developed. The case appeared to be almost hopeless, but under injections of caffeine there was slight improvement and a gradual recovery, with the exception of a paralysis of the right arm and leg. T. H. Walker (Lancet, Nov. 18, 1905).

TREATMENT OF CAMPHOR POISONING.—The first step is to empty the stomach as soon as possible by means of an **emetic** or, better, by washing out the organ with **warm saline solution**, which itself promotes emesis. **Sugar** has been recommended as an antidote on theoretical grounds; it might then be given in solution in the hope that the harmless glycocamphoric acid will be formed.

Case of camphor poisoning in a young woman who took about 15 Gm. ($\frac{1}{2}$ ounce) of camphor suspended in water, probably to produce abortion. Two hours later a violent headache developed, with vomiting, convulsions, and later coma. The pulse was full and strong, and respiration rapid. Excitement increased until the patient became unconscious. The **stomach** was **washed** out several times and **chloral** and **bromide** were administered. After several days' illness she entirely recovered. The fatal dose of camphor is 2.5 to 7 Gm. ($\frac{1}{2}$ to $1\frac{1}{2}$ drams), and the writer attributed the recovery to the fact that the patient had eaten a hearty dinner composed largely of hydrocarbons a short time after taking the poison. By this means there was formed in the intestine glycocamphoric acid, which is not poisonous. He recommends in an overdose of camphor, therefore, that the patient be given large doses of **sugar** as an antidote. Berkholz (St. Petersburg med. Woch., Nu. 51, 1898).

The influence of camphor on the nervous system, especially in view of the tendency to convulsions, renders the **bromides** and **chloral hydrate** of at least theoretical value; but the same plea would cause **strychnine** to be contraindicated, though generally used. On the whole, the treatment of poisoning by camphor is at present on an **unsatisfactory** foundation.

Chloroform has also been used to check the convulsions, but the results obtained do not seem to warrant its administration.

THERAPEUTICS.—Camphor is considerably used, and on good ground, as a circulatory and respiratory stimulant in **collapse**, **heart-failure** where the myocardium is mainly at fault, and general **adynamia** due to abnormal vasodilation, as in **shock** and **exhaustion**. The most efficient mode of administration in emergency cases is 8 minims (0.5 c.c.) of camphorated oil (*linimentum camphoræ*) hypodermically every fifteen minutes four times if needed, watching the patient closely, and ceasing the injections as soon as the patient is restored.

Camphorated oil has long been used in the asthenic stage of infections, the exanthemata, **scarlatina**, **measles**, **small-pox**, etc., and also in **pleuropneumonia**, **lobar pneumonia**, **pulmonary edema**, **infectious endocarditis**, **typhoid fever**, **influenza**, etc., owing mainly to the favorable reports of Huchard, Schilling (1895), and others. Recently, however, Seibert pointed out that, in **pneumococcic infections** at least, camphorated oil exerted a direct destructive action upon the pathogenic organism. He found that it reduced the toxemia gradually until practically normal conditions were reached three or four days after the first injection. This favorable result and the absence of crisis occurred in every case. To the bactericidal action of camphor was probably due also the favorable results noted by Huchard, Schilling, Thassia, Alexander, and others.

In 21 cases of pneumococcic **pneumonia**, 12 c.c. (3 drams) of a 20 per cent. camphorated oil were injected

every twelve hours in adults, and 6 c.c. (1½ drams) in children (the youngest being 4 years of age), irrespective of the size and weight of the patient, the intensity of the toxemia, and the extent of the local process. In 4 of the next 16 cases the limitations of this treatment were observed. A sudden rise of temperature in 2 patients on the second and third days of treatment, respectively, proved to be due to pneumococcic nephritis, promptly subdued by appropriate doses of hexamethylenamine, while the camphor injections were continued and resulted in speedy recovery. In 2 cases of severe **pleuropneumonia** from the onset (aged 13 and 28, respectively) the camphor reduced the general toxemia markedly, but did not prevent the accumulation of pus in the pleura, necessitating rib resection in the one on the fourth, and in the other on the eighth, day after the initial chill, pneumococci in pure culture being found in the exudate, and both patients recovering. The one death among the 37 cases of **pneumonia** so treated occurred in a man 68 years of age, weighing 200 pounds, with fatty heart, attacked by pneumococcic invasion of both lower lobes, marked toxemia, and copious bloody sputum. Although early camphor injections had the usual good effect on the sensorium, the temperature, and the respiration, his flabby heart began to give out on the fifth day, resulting in fatal pulmonary edema on the sixth.

During the last four years the writer has made many hypodermic injections of 10 per cent. salicylic acid solutions in 20 per cent. camphor oil in **rheumatism**, and has observed the prompt destruction of meningococci in the blood of a 2-year-old patient by a 3 per cent. salicylic acid solution in a 30 per cent. camphor oil, 5 c.c. (1¼ drams) being injected every forty-eight hours.

The writer's observations have established the following facts: (1) that 10 c.c. (2½ drams) of a 30 per cent. camphorated oil (equal to 36

grains—2.3 Gm.—of pure camphor) injected hypodermically to 100 pounds of human body weight every eight to twelve hours do not produce symptoms of poisoning; in fact, are harmless; (2) that much larger doses (to the body weight) in rabbits are equally well borne, and (3) that *these quantities of camphor materially assist in overcoming pneumococcic toxemia*, and (4) that the earlier this treatment is resorted to the better the results. Seibert (Med. Record, April 20, 1912).

The addition of camphor to digitalis in the treatment of **pneumonia** has also been found to enhance the beneficial effects of the latter drug in this disease.

The writer recommends the use of a combination of digitalis and camphor in the treatment of **croupous pneumonia**. It is noted that digitalis acts as an antiphlogistic in pneumonia, as by stimulation of the vagus the diastole is prolonged and the venous circulation through the lungs facilitated. By this depletion of the overfilled lungs the exudation in the alveoli is lessened. He also points out that, although the various active principles of digitalis cause contraction of the arterioles and hence an increased peripheral arterial pressure, it has been proved by Mellin that this does not occur in the pulmonic system except by intravenous injection of digitalin. Therefore the action of digitalis becomes doubly useful in pneumonia; but to have this effect, it must be given early and in large doses. To counteract the danger of large doses of this drug the author combines the digitalis with camphor, on account of the latter's known power to stimulate the nervous apparatus of the heart, as well as its stimulating action on the vasomotor and respiratory centers. The writer uses a 1 per cent. infusion of digitalis with an equal quantity of camphor emulsion [the camphor emulsion of the Norwegian Phar-

macopœia has the following composition: Pulverized camphor, 1 part; mucilage of acacia, 40 parts; distilled water, 159 parts] in tablespoonful doses every hour during the first twelve hours, and afterward every other hour. Each tablespoon will therefore contain 0.15 Gm. ($2\frac{1}{4}$ grains) of digitalis and about 0.0375 Gm. ($\frac{1}{2}$ grain) of camphor. He gives half this dose to children between 10 and 15 years of age, but has not used the drug for children under 5 years. Quisling (New York Med. Jour., from Brit. Med. Jour., May 28, 1910).

Camphorated oil injections into the peritoneal cavity have been recommended by Höhne and Pfannenstiel to prevent **peritonitis** in laparotomy for severe infections, the purpose being to increase the bactericidal activity of the patient.

In the course of a year 172 laparotomies were performed by the writer. In 79 of these, intraperitoneal injections of sterilized camphorated oil were administered. He introduced the oil at the time of the operation, or, if a glass drainage-tube was used, immediately after the operation, to the extent of 50 c.c. ($12\frac{1}{2}$ drams). K. Kolb (Hospital, Jan. 21, 1911).

The following formula is used by the writer in his surgical cases:—

R *Camphor* ʒij (12 Gm.).
Purified olive oil .. ʒix (36 c.c.).
M. Fiat mistura.

After the camphor is dissolved the oil is filtered. Twenty c.c. (5 drams) are injected twice daily when the heart action is feeble. The results, even in grave septicemia, have been excellent, and the dose has been raised to 100 c.c. ($3\frac{1}{2}$ ounces) daily without unfavorable symptoms. The camphor is rapidly eliminated through the lungs. P. Baudet (Province médicale, March 11, 1911).

To avoid the many drawbacks to the usual method of introducing camphor, a very slow and often in-

complete absorption, and the very small amount of the drug which enters the circulation, the writer advises intravenous injections of a saturated aqueous solution, Ringer's saline solution being used as medium. The amount of camphor injected each time varies from 10 cg. ($1\frac{1}{2}$ grains) in 75 c.c. ($2\frac{1}{2}$ ounces) solution to 30 cg. (5 grains) in 300 c.c. (10 ounces) water, to which 1.5 c.c. (24 minims) alcohol is added. The total amount of camphor utilized is thus reduced without interfering with its effective physiological action. The solution is prepared by simply shaking powdered camphor in Ringer's artificial serum, the resulting concentration being 0.142 per cent. H. Leo (Deut. med. Woch., Mar. 14, 1918).

Camphor is extensively used in Europe in genitourinary disorders and particularly in **ischuria**, **strangury** due to the use of cantharides, in the **chordee** accompanying **gonorrhea** or **spermatorrhea** due to general asthenia, abnormal **sexual excitement**, and in **cystitis** of bacterial origin accompanied by acidity of the urine.

Camphor having been employed abroad as a urinary antiseptic, the writer requested a specialist of genitourinary diseases to try its efficacy. The latter obtained good results in a number of cases of **cystitis** with an acid urine, but no amelioration in those in which this excretion was alkaline. Tyrode (Boston Med. and Surg. Jour., June 11, 1908).

Camphor has long been used in various forms of **diarrhea**, especially those forms termed **choleraic**, **summer**, or **tropical diarrhea**, and **cholera morbus** in which prostration and coldness of the surface occur. It is also recommended in **dyspepsia** and **gastrodynia**, but in small doses, and as a carminative in the **flatulent colic** of infants.

It has been considerably employed in nervous disorders, especially in **hysteria**, in the varieties of **insanity** due to **asthenia**, particularly in **melancholia**. It is contraindicated, however, in all conditions attended by cerebral excitement, particularly in **plethoric** subjects. **Dysmenorrhea** and the **after-pains** of parturition are greatly benefited.

The glandular secretions are markedly influenced by camphor. While it enhances the activity of the sweat-glands under normal conditions and is thus useful in **colds**, **coryza**, etc., it tends to check the **night-sweats** of **tuberculosis**, because these are due to relaxation of the spiral muscles of the sudorific tubules, which camphor stimulates. The most satisfactory results are obtained by giving it in oil, as in the treatment of pneumonia. Its bactericidal action is thus brought into play. It tends also to check or prevent **hemoptysis** when used in pulmonary tuberculosis.

Another useful indication for camphor is in **lactation** when it is necessary, as in obligatory **weaning**, to arrest the secretion of milk. It is also useful in the treatment of **salivation** from any cause.

Camphoric Acid.—This preparation has been used mainly in the treatment of **night-sweats** of **pulmonary tuberculosis**. To obtain its best effects, it is said, 15 to 30 grains (1 to 2 Gm.), according to the strength of the patient, should be given dry on the tongue and washed down with a glass of milk or water two or three hours before the sweating usually occurs. Experimental work on camphoric acid has given negative results, and some deny it any anhydrotic action clinically.

The other indications of camphoric

acid are similar to those of camphor, but it has been found more efficient in the treatment of catarrhal disorders of the respiratory tract, **acute coryza**, **pharyngitis**, and the **pharyngotracheitis** which often follows winter colds. A $\frac{1}{2}$ to 2 per cent. solution, used with the atomizer while inhaling vigorously, is sometimes very efficient. It has been vaunted as a preventive of **catheter fever**.

Camphoric acid is a **preventive** of the fever following intravesical and intraurethral operations. Especially after Bottini's operation this complication appears to be frequent. Camphoric acid administered for several days before the operation in doses of 1 Gm. (15 grains) three times daily will prevent the fever, unless some complication like epididymitis, etc., is responsible for the rise of temperature. D. A. Freudenburg (*Gazzetta degli osped. e delle clin.*, No. 38, 1903).

Monobromate of Camphor.—This preparation has been deemed superior to camphor in the treatment of **infantile diarrhea**, especially in the threatening form, **cholera infantum**, having proven more efficient than many other remedies in the stage of collapse. Being not only a potent cardiovascular stimulant, though a sedative of the cerebrospinal and peripheral nervous system, but also an antiseptic, it favors recovery.

[Though it seems difficult to reconcile the facts that a drug can simultaneously be a cardiovascular stimulant and at the same time a sedative of the cerebrum, cord, and peripheral nervous system, the process becomes plain when it is accounted for from my viewpoint, viz., that the vascular constriction produced by camphor and its preparations reduces the caliber of the arterioles which supply the brain, cord, and nerves and by thus reducing the arterial blood supplied to these

structures diminishes their irritability in proportion. C. E. DE M. S.]

In neuroses it is also of value, particularly in **epilepsy**, **hysteria**, **nymphomania**, and **chorea**, in which the cerebrospinal centers are hyper-sensitive. Being possessed of hypnotic properties, camphor monobromate is of special value in these cases when **insomnia** occurs as a complicating factor.

Camphorated Tincture of Opium.—

The many uses to which this preparation is devoted depending mainly upon the opium it contains, its therapeutic applications will be studied under **OPIMUM**. Its specific action in **cholera morbus**, which it sometimes arrests in a few moments, warrants, however, a special mention in the present connection.

Local Uses.—Camphor and its preparations, the camphor liniment, the soap liniment, and spirit, are used extensively externally for **bruises**, **sprains**, and **myalgia**. In the two latter the liniment, rubbed into the tissues by gentle massage, relieves pain and promotes resolution.

In cutaneous diseases camphor is especially valuable for the relief of **pruritus**. In **pruritus ani**, for example, 1 dram (4 Gm.) of powdered camphor to 1 ounce (30 Gm.) of vaselin, the ointment being applied about and within the anus, is very beneficial. The pain, tension, and burning of vesicular, exudative, and pruriginous affections, such as **eczema**, **pemphigus**, **erysipelas**, and **intertrigo**, are relieved, according to Phillips, by a powder composed of camphor, 40 grains (2.6 Gm.), and oxide of zinc and powdered starch, of each, 1 ounce (30 Gm.). **Furuncles** may be aborted if spirit of camphor

is applied early on cotton. **Ulceration** following **carbuncle** may also be checked and caused to heal.

The writer always uses for **wounds**, **bruises**, **sprains**, etc., alcohol, or spirit of camphor and water, in preference to any other applications. On open wounds one or the other is preferable in every particular to bichloride of mercury or any other antiseptic solution. Case of **ulceration** of large dimensions on the nape of the neck, following a very severe case of **carbuncle**, in which pure alcohol (95 per cent.) first, and subsequently spirit of camphor and water, worked wonders. Without their use skin grafting would have been required and perhaps not been successful. Beverly Robinson (N. Y. Med. Jour., April 6, 1912).

Camphor-chloral is mainly used nowadays, applied topically, for the relief of **neuralgia**, while *camphor-phenol* has been found very useful to assuage **toothache** due to an exposed and inflamed pulp, and also as an effective agent for the local treatment of **ulcerations**, especially those of the mouth, i.e., in the various forms of **stomatitis** and **glossitis**.

Prof. Cleland, of Glasgow, called the writer's attention to the efficiency of a mixture of pure carboric acid crystals and camphor in equal parts as a local application for small **ulcers**, such as those which frequently occur in the mouth. There is little destruction of tissue, and beyond a slight smarting at the time of application no unpleasantness. The ulcers themselves rapidly heal after the application. The supposed loss of disinfectant properties was found to be incorrect by culture experiments at the Bureau of Microbiology. B. Cleland (Austral. Med. Gaz., Jan. 2, 1910).

C. E. DE M. SAJOUS

AND

L. T. DE M. SAJOUS,
Philadelphia.

CANADIAN HEMP. See APOCYNUM.

CANCER.—GENERAL CONSIDERATIONS.—In no field of medicine is there greater need for a careful collection of statistics, for painstaking research, and for a judicious correlation of associated facts than in that of cancer. Though the death rate is not so high as in other diseases, notably tuberculosis, it is sufficiently great to afford it few rivals, and, when other features of the disease are considered, one may well doubt whether it is not entitled to the first place among the most dreaded maladies which afflict mankind. In cancer there is practically no appreciable tendency toward spontaneous recovery, and but little can be done to check its progress when far advanced, although the disease can be often cured in its earlier stages by proper and adequate treatment, to be mentioned later. Unfortunately, owing to prejudice and the deficiency in the education of the general medical profession, it happens that the removal of cancer in its incipient stages is accomplished in only a small proportion of cases, and too often operation is reached only when it is already too late to absolutely eradicate the disease.

Frequency of Cancer.—The actual frequency of cancer and its ethnological distribution are matters of considerable importance. It is difficult, however, to draw correct conclusions on this subject, owing to the unreliable manner in which many of the vital statistics are obtained. This is true even among many of the European countries. One fact, however, has been definitely demonstrated by statistics, namely, that a

higher mortality from cancer coincides with a greater accuracy in the compilation of the causes of death; undoubtedly, this fact explains in a large measure the prevalent belief that cancer occurs with the greatest rarity among the uncivilized races.

In the United States it is estimated that 5 per cent. of all deaths after the age of 30 are from cancer, and it may be conservatively said that about 90 per cent. of its victims die therefrom.

In England, out of a total of 141,241 deaths of males over 35 years of age, in 1907, 12,695 died of cancer, and, out of 140,607 deaths of females over 35 years of age, 17,671 died from cancer. Therefore, of those living to 35 years of age or over, 1 man out of every 11, and 1 woman out of every 8, dies of cancer. The crude death rate from cancer in England is 0.092 per cent. of the living population; in Wales and Ireland it is 0.079 per cent. Much greater accuracy in regard to the recording of vital statistics is obtained in England than in Ireland or Wales.

In Switzerland still greater accuracy prevails; medical inspection of the dead is customary, and autopsies are performed in 25.7 per cent. of deaths. There the crude death rate from cancer is 0.129 per cent.

In Holland great care is also exercised in the recording of vital statistics, and coinciding with this we find a correspondingly high rate attributed to cancer, namely, 0.101 per cent. The Prussian statistics are acknowledged to be not very accurate, and the death rate from cancer there is 0.070 per cent.

These figures contrast strongly with those from Spain and Hungary, for which the percentages are, re-

spectively, 0.044 and 0.04 per cent., and still more strongly with the percentage of 0.011 per cent. for Servia, where incompetent and ignorant people certify as to the causes of death. In some of these latter countries the death records are intrusted to laymen and even laywomen, and in Catholic countries the duty is very apt to fall on the parish or district priest. To illustrate how inaccurate the returns may sometimes be: Prinzing cites that in one case an ignorant peasant returned all deaths as due to cardiac failure, and another in Tilsit attributed 50 per cent. of the deaths to diphtheria.

[These facts are further illustrated by the more recent statistics which Buday reported at the Second International Congress on Cancer, held in Paris in 1910. They represent the number of individuals dying of cancer for each 10,000 of the living population:—

Switzerland	1907	12.5
Denmark	1907	12.2
France	1906	10.0
Sweden	1890-98	9.96
Holland	1903	9.9
Norway	1906	9.75
England	1907	9.08
United States		7.06
Austria	1905	7.5
Germany	1907	7.45
Hungary	1904	7.0
Italy	1906	6.09
Belgium	1907	6.02
Japan	1905	5.3
Spain	1903	4.4
Portugal	1904	2.37

H. H. JANEWAY.]

Apparently the death rate from cancer is less in the South and greater in the larger cities than in the country, but this difference may only be apparent on account of the inaccuracy in collecting statistics. In Brazil the death rate in 1894 to 1898 was 0.41. In Rio de Janeiro, in 1894 to 1898 it was

2.81. In Portuguese Guinea and the neighboring islands cancer has been frequently reported (A. Neses).

In Lapland cancer is rare; very few cases have been reported. In Africa, Egypt, and Tunis it is also rare. In Australia the death rate from cancer is fairly high. In Tasmania it is 5; in New Zealand, 1907, 9.3; in Victoria States, 6.09 per 10,000 of the living population.

The question of a yearly increase in cancer is an important one, and one upon which there has been considerable difference of opinion. Those authors who have based their conclusions upon the vital statistics state that the death rate from cancer is increasing from year to year. W. Roger Williams ("Natural History of Cancer," 1909) states that there has been a yearly increase in the cancer death rate from 3 to 5 per cent. during the past twenty or thirty years.

Coley ("Surgery, Gynecology, and Obstetrics," pp. 591 to 597, June, 1910) has collected a large number of statistics from which he believes that there is a steady increase in the death rate from cancer. According to the Widows' Life Insurance Company the following table represents the proportion of deaths due to cancer to the total mortality:—

For 29 years from	1815 to 1844,	0.93
" 13 " "	1845 " 1858,	1.79
" 7 " "	1859 " 1866,	3.00
" 6 " "	1867 " 1873,	4.56
" 6 " "	1874 " 1880,	4.93
" 6 " "	1881 " 1887,	5.44
" 6 " "	1888 " 1894,	6.88

[The German Life Insurance Company gives the following statistics:—

From 1889 to 1895 an increase of deaths from cancer from 3 to 7 per cent. among males, and 11.4 per cent. among females. From 1870 to 1906 the Ætna Insurance Company record show that the death

rate from cancer has increased from 2.6 to 7.3 per cent. Roy F. Edwards (*Medical Record*, 1909, lxxvi, 1030) has shown an increase per 100,000 inhabitants from 48.3 in 1883 to 58.7 in 1885, and to 77.3 in 1907.

In Switzerland the rate has risen from 114 in 1889 to 132 per 100,000 in 1898. In Paris the death rate from cancer per each 100,000 of the population in 1865 was 84. In 1870 it was 91; in 1810, 95; in 1890, 108, and, in 1900, 106.

In Australia in 1851 the death rate was 14; in 1861 it was 19; in 1871, 25; in 1881, 32; in 1891, 45, and in 1901 it was 57 per 100,000 of the population.

In the United States the general increase in the death rate from cancer per 100,000 inhabitants between the years 1890 to 1900 was 12.1.

A comparison of the death rate of cancer and that of pulmonary tuberculosis is interesting. In 1890 there died from pulmonary tuberculosis in the United States 102,199 people, a proportion of 12.146 for each 100,000 of all cases of death. In 1900 111,058, or 10.688 for each 100,000. Of pneumonia there died in 1890 76,496, or 9.091 for each 100,000, and, in 1900, 105,971, or 10.198 in each 100,000. Of cancer in 1890 there was 18,536, or 2.203 for every 100,000 for all cases of death. In 1900, 29,475, or 2.837 for 100,000 for all cases of death.

Frief ("Cancer Statistics," I. D. Jena, 1904), after quoting in his discussion upon the increase of cancer from Wells, Koll, Barker, Park, Prinzing, and Rosenfeld, challenges their results on the ground of accuracy and by comparison with his own more accurate figures for the city of Breslau. Spencer Wells finds that during twenty-six years in England the death rate from cancer had increased from 360 to 606 for each million. Kolb finds in England, in 1851 to 1890, an increase in the death rate from cancer 86 per cent. Fordyce Barker, of New York City, finds an increase in cancer from 400 to 530 between the years 1875 to 1885. In Switzerland, between the years 1889 and 1898, there had been an increase of 2 per cent. Prinzing, who had collected very exact statistics in Italy, found only a small increase in that country. In Holland there had been no increase between the years 1898 and 1900.

Rosenfeld reports that cancer had doubled

during the last*twenty-five years in Austria. In 20 of the States of the German kingdom, in the years between 1897 and 1899, there has been an increase of 7.2 per cent., and this represents three times as great an increase as the increase in the population for the same time.

Reiche (*Deut. med. Woch.*, 1900, xxvi, 120) found in Hamburg only an insignificant increase in cancer between the years 1872 and 1898. Loth (*Korrespondenzbl. Aerztverein und Thüringen*, No. 12, 1901) has found an increase in cancer of 23.8 to 57.8 to each 100,000 of the population in the city of Erfurt during the last twenty years. Frief quite correctly questions the accuracy of these statistics. We cannot deduce conclusions from statistics of life-insurance companies, and from certain countries such as Austria, and from some of the States in Germany, or even in England; certainly not in the early days. Frief has found in the city of Breslau, which has kept very accurate statistics during the past twenty-five years, an increase of cancer during this period of only 0.45 per cent., and that this increase has not changed during the past nineteen years. Cancer of the breast and uterus has not increased during this time, while cancer of the gastrointestinal tract has.

If, now, we turn to the autopsy table, statistics show that from this source cancer is not increasing at the present day. For instance, Riechelman (*Berl. klin. Woch.*, 1902, xxxix, 728; 758) has found for the years 1895 to 1900 practically no increase in the number of cancer cases.

Year	Autopsies.	Cancer cases.	Per cent.
1895 to 1896	1288	103	8
1896 to 1897	1130	125	11
1897 to 1898	1107	104	9
1898 to 1899	1254	125	10
1899 to 1900	1310	118	9
1900 to 1901	1337	116	8

Orth (quoted from Buday, Second International Congress on Cancer at Paris, 1910) has found, for Berlin, during the year 1875, that 4.9 per cent. of the number of autopsies were cancer cases. During the year 1885 there were 7 per cent. During the year 1907, 14.11 were cancer cases. He concludes that

there is a slight increase in the death rate. Lex (quoted from Buday, Second International Congress on Cancer at Paris, 1910), of Heidelberg, found, during the years 1870 to 1879, that 6.75 of the autopsies proved to be cancer, and between the years 1900 and 1907 9.13. Rieck, of Munich, between the years 1854 and 1863, found that 7 per cent. of the autopsies were cancer cases, and between the years 1894 and 1903 12.5 per cent. Steinhaus (quoted from Buday, Second International Congress on Cancer at Paris, 1910), of Brussels, between the years 1888 and 1897, found that 8.6 per cent. of the autopsies were cancer cases, and between 1898 and 1907 9.07 per cent. Feilchenfeld (quoted from Buday, Second International Congress on Cancer at Paris, 1910, 89, and Redlich) has found that for Berlin, at the Urban Hospital between 1895 and 1900, 13.24 cancer cases, and between 1900 and 1905 13 per cent. of the autopsies were cancer cases. Buday, at Kolozsvár Hospital, found that, from 1870 to 1888, 8 per cent of the autopsies proved to be cancer. In 1889 to 1905 there were 9.91 per cent.

Rieck ("Inaugural Dissertation," Munich, 1904) also gives the following statistics: From 1854 to 1902 there were 25,105 of autopsies performed in Berlin. Of this number, 2410 were upon cancer cases (9.6 per cent.). Of these, 885, or 6.06 per cent., were upon male patients, and 1524, or 14.56 per cent., were upon female patients. The percentage of cancer cases increased during this period from 7 to 12 per cent.

Nobiling ("Statistik d. bösartigen Geschwülste a. d. Sektionsmaterial d. path. Institut d. Krankenhauses München in den Jahren 1908," Zeitschr. f. Krebs., 1910-11, x, 286) has given the following table, comprising 1371 autopsies between the years 1903 and 1909. He notices only a slight increase in cancer cases:—

Year.	Deaths.	Carcinoma.	Per cent.
1903	394	51	12.9
1904	396	54	13.6
1905	441	62	14.1
1906	432	76	17.5
1907	493	100	20.0
1908	643	111	17.3
1909	728	101	14.0

Year.	Carcinoma.		Sarcoma.	
	Male.	Female.	Male.	Female.
1908	40	71	4	5
1909	40	61	6	4

H. H. JANEWAY.]

These statistics, taken from the autopsy table, cause some doubt to exist as to how real the alleged increase of cancer is. Almost all of the more recent authorities believe that, whatever increase there is, is limited to an increase of cancer of certain organs, while there is no increase in other organs. Bashford has shown for England that cancer of the uterus is diminishing rather than increasing, while cancer of the gastrointestinal tract has increased slightly. He states that for males the main increase falls on the alimentary tract, especially the stomach. The liver and gall-bladder show no increase. For females the increase, although it also falls mainly upon the alimentary tract, affects also the breast, while the uterus, ovary, liver, and skin show no increase. The accuracy, therefore, of our data is a consideration of great importance in estimating both the frequency and yearly increase of cancer.

ETIOLOGY.—The etiology of cancer includes the consideration of a number of factors, all of which have a bearing upon our ideas as to its causation. These will be considered seriatim under the following heads:—

1. The occurrence of cancer in the animal and plant kingdoms.
2. Its distribution according to race and country.
3. Whether or not there is any predilection for certain localities in the same country or city.
4. Its relation to sex and age.

5. The frequency, with which the various organs and tissues are affected.

6. The influence of heredity in its incidence.

7. The influence of occupation and diet upon its development.

Cancer in Animals.—The close similarity of animal cancer to human cancer has been demonstrated, and certain important facts have been developed, as a result of the cultural propagation of its cells by a process of continued transplantation.

The precancerous lesions are produced by some habit of life condition which causes chronic irritation. A close study of the habits of civilized man as contrasted with primitive races and lower animals, in which similar lesions are conspicuously rare, is necessary. W. J. Mayo (Annals of Surg., June, 1914).

In a brief study of some blood changes in rats on various diets, the writer found the effect of these diets on the blood and on 1, growth and nutrition of rats; 2, takes, growth energy, and metastases of the experimental tumor; 3, length of life of animal after inoculation. The investigation showed that all diets which gave in normal animals an approximately normal growth curve, grew large tumors with high percentage of takes, all diets which depressed the growth curve, retarded or prevented tumor growth. A study of blood of rats on these diets showed no change in numerical count of red and white cells, but a decrease in number of lymphocytes in all diets stimulating cancer growth, and an increase in all diets which retarded tumor growth. From the work it would appear that cholesterol is a factor which, while of little or no nutritive value, favors tumor growth when conditions favorable to its initiation are present. E. P. Corson-White (Trans. Penna. State Med. Soc.; N. Y. Med. Jour., Mar. 1, 1919).

A squamous cell carcinoma has been found in the *Gasterostens spinachia*, and an osteosarcoma has been observed in the operculum of a cod. Carcinoma in the thyroid of the trout is of comparatively frequent occurrence; since the first authentic case was discovered by Mr. Gilruth, over 2000 additional ones have been reported. Mr. Smallwood, of Syracuse University, has described a carcinoma of the kidney of a frog, and there have been reported 2 cases of carcinoma of the skin in the frog. A carcinoma of the glands of the skin of the *Triton cristatus* has been reported.

Plehn (Second International Congress on Cancer at Paris, 1910) states that there are few real tumors in reptiles or amphibians. In fishes the number of growths of various kinds is very great.

Peyton Rous (Jour. Amer. Med. Assoc., 1910, 1v, 1805; 1911, lvi, 198 and 741) has described a spindle-cell sarcoma growing in Plymouth Rock chickens, and has been able to develop such a degree of malignancy in this tumor that it can be transplanted successfully in 85 per cent. of the purebred Plymouth Rocks. A feature of very great significance in connection with these tumors is that they are capable of being transmitted by a cell-free filtrate.

Among mammals, malignant tumors are found with rather surprising frequency; as might be expected, they occur most often among those animals with which we are most familiar, the horse, dog, mouse, and rat. One cannot but believe that systematic search would reveal a yet more widespread distribution of cancer throughout the animal kingdom. When the Imperial Cancer Research first started its in-

vestigations, doubt was expressed as to whether any instances of spontaneous tumors would be encountered among mice; since that time up to the time of the report 1000 cases of cancer have been presented to the laboratory.

The identity of these animal tumors with human cancer has often been questioned.

Von Hansemann is the most important authority who denies that these animal growths correspond to human cancer. Notwithstanding his high authority, we cannot agree with his reasons. Whether these new growths, particularly those growing in rats and mice, represent the same pathological condition as true human cancer is a matter of considerable importance.

Upon the identity of the two forms of growth will depend not only many facts of prime importance in tumor growth, but also our ideas of immunity in cancer and of the susceptibility of malignant new growths to a more ideal method of treatment than at present exists.

Apolant (*Berl. klin. Woch.*, 1912, xlix, 495) undertook very successfully in our own mind, to answer von Hansemann's arguments.

In almost every respect, though there are quantitative differences, the features of animal cancer answer to our criteria for the disease as it occurs in the human race. This includes their histological structure, their invading characteristics, their clinical course, and finally their ability to form metastases. The latter is, perhaps, the most important of all.

Hanau, as early as 1889, described metastases in the lymph-nodes of a rat with a primary epithelioma: this tumor he successfully transplanted. Borrel, in 1903, recorded pulmonary metas-

tases in a large proportion of the mice spontaneously developing cancer. Borrel and Haaland described later an epithelioma developing in the paw of a mouse, and showed that the metastases originated in minute emboli, which became lodged in the branches of the pulmonary artery and then grew backward. Leon Michaelis, who described a carcinoma in a rat, recorded metastases in the transplanted tumors. In the transplantable sarcoma of the rat described by Flexner and Jobling, metastases also occurred. Among the tumors resulting by inoculation from the seventy spontaneous primary tumors which have furnished the working material for the laboratory of the Imperial Cancer Research Fund, 50 per cent. have produced metastatic growths.

In the clinical course of these tumors there is a striking similarity to human malignant growths. This is noted in the character of the tumor elements, in their rapidity of growth, and in their invading characteristics. It is also shown by the large size which they attain, the frequent recurrence after operation, and the rapidity with which recurrence is likely to follow after the first operation, as compared to the rather long period of quiescence succeeding a second operation.

The employment of these tumors in various modes of experimentation has furnished a new series of facts which are applicable to the problems of human cancer. Among the most interesting of these are the conditions under which these tumors can be transplanted into other animals. These conditions concern the age and the adaptability of the inoculated animals, the quantity and degree of comminution of the material used for inoculation, and, what

is most important, the particular period of growth in which the tumor may be at the time of inoculation. Regarding the age of the inoculated animals, in general, younger mice are more susceptible to successful implantation than older ones: but there is also noticed, aside from youth, a tendency for the tumor tissue to adapt itself more readily to animals of approximately the same age as those from which the tissue for transplantation is taken.

Tumors are much more readily transplanted into native mice than into mice from other countries. On the other hand, after a tumor has been growing for a longer or shorter time in a mouse of a foreign country, it loses its ability to again grow so well in a mouse from the same country as that to which the original host of the tumor belonged. Adaptability, therefore, is a very important characteristic of cancer cells.

The subdivision or comminution of the material used for transplantation greatly affects the chances of successful inoculation. The method adopted by the laboratory of the Imperial Cancer Research Fund is more successful than other methods utilized. In this laboratory the cancer material is divided by a specially constructed hashing machine devised by Haaland, and certain definite amounts of the tissue thus cut are injected subcutaneously, without dilution. This method is more successful than when larger pieces are implanted, or when the cancerous tissue is ground up in a mortar, and it also permits of more accurate dosage.

In a particular form of tumor in mice (hemorrhagic tumors), which Ehrlich succeeded in transplanting successfully only once in 500 times, Gierke, of the London laboratory, has been able to inoculate easily; in one series he

obtained even 100 per cent. of successes. Of the total number of spontaneous tumors, Ehrlich has succeeded in transplanting only 14 per cent., whereas 80 per cent. have been propagated by the workers in Bashford's laboratory. Animal tumors, at least in the form of carcinoma in mice, show great fluctuations in the percentages of successful inoculations during consecutive transplantations. The fluctuations occur periodically in wave-like curves, and corresponding with them are similar fluctuations in the rapidity of growth of the tumor.

Such fluctuations in malignancy strongly suggest accompanying biological alterations of the tumor-cells during successive transplantations; extensive changes of this kind have been shown to occur by Murray in certain epithelial cancers of mice. These cancers will so change their morphology that at one time they conform to an adenomatous type, and at another time present the appearance of epithelial tumors, associated with excessive keratinization, and yet again acquire adenomatous characteristics.

The most interesting change of all which carcinoma in mice undergoes is a transition into sarcoma. This, however, cannot be spoken of as a metaplasia of the epithelial cells; it is rather a replacement of one form of tumor by another, which spontaneously develops from the transplanted stroma. This has been proved by microscopic examinations made at intervals of eighteen to forty-eight hours after transplantation. In the process of transition of carcinoma into sarcoma there is first formed a mixed tumor, and in the development of such a growth the cells of the transplanted connective-tissue stroma no longer de-

generate, but begin to proliferate and show numerous mitoses, even within twenty-four hours after transplantation.

Many attempts have been made to transplant these tumors into human beings, and, with three or four claimed exceptions, these attempts have universally failed. Of 400 attempts made by Sticker (*Zeitschr. f. Krebsforsch.*, 1908-09, vii, 55) to inoculate human cancer into mice and rats no case was successful. Metchnikoff has never succeeded in inoculating human cancer into apes. It is also impossible to inoculate the animal tumors into animals of different species.

Salivary tumors from a Japanese mouse cannot be transplanted into a white mouse. Jensen has transplanted a tumor of a white mouse into a house mouse, but did not succeed in transplanting it into a field mouse.

In a series of 12,000 necropsies on the bodies of mice there were found 87 mice with neoplasms meeting all the criteria of sarcoma. Metastasis was observed in 23 cases, or 26.4 per cent., the osteoid sarcomas leading with 75 per cent. metastasis occurred in only 13 per cent. of the spindle-cell sarcomas. Lungs, liver and lymph nodes showed most of the metastases. In all respects these sarcomas of mice correspond with the sarcomas of men, although the authors found no examples of melanoma, multiple myelomas, or myeloid sarcoma. As with human tumors, mouse sarcomata frequently arise at the site of a trauma, and this has been observed in 11 of the writer's series. It is evident to them that they have no knowledge of how many of the other mice had received injuries at the point at which they subsequently developed a sarcoma, for the life of a mouse is beset with many accidents and deeds of violence. Especially among the males, wounds are often received in fighting. Slye,

Holmes and Wells (*Jour. Cancer Research*, Jan., 1917).

GEOGRAPHICAL DISTRIBUTION.

—Concerning the geographical distribution of cancer, tables have already been given in discussing its frequency. We have seen that the accuracy with which these statistics have been collected materially affects our ideas of the relative frequency of cancer not only in different countries, but also in different races in the same country.

Another factor which accounts for the greater frequency of cancer in England, Germany, and the United States in later years as compared with very much earlier periods is the steadily increasing average length of life. Cancer is a disease which belongs peculiarly to the later years of life, and, for this reason, more individuals are permitted to develop cancer because there are more living at the cancer age than there were some years ago. All the above considerations explain in a good measure the prevalent idea that cancer is infrequent in Japan, China, India, and very rare among uncivilized races.

Statistics indicate, however, that, out of a total of 959,126 deaths occurring in Japan for the year 1901, 24,598 were due to malignant new growths. The population of Japan for that year was 45,227,404, and the crude death rate from cancer was, therefore, 0.056 per cent.; between the years 1899 to 1903 it was 0.049 per cent. By these figures, therefore, cancer would appear to be more frequent in Japan than in Spain, Servia, or Hungary, and only one-half as frequent as in England, and, if allowance is made for variation in the reliability of the records of these countries, it is probably as frequent as in England.

The statistics for Japan were collected by Baelz, at the suggestion of the workers of the Imperial Cancer Research Fund, and are all the more remarkable when considered in connection with the remark of Baelz at the time the investigation was requested. He stated at that time "without doubt cancer is much rarer in Japan than in Europe, and the correctness of this opinion is demonstrated by the relatively large number of cases which occur among the small number of European inhabitants in Japan, as contrasted with the rarity with which the disease is observed among the natives themselves."

In India, out of a population of 300,000,000, with all the inaccuracies that exist in the collection of vital statistics (and recognizing the comparatively small proportion of the population, especially among women, who seek treatment at the European hospitals in that country), over 2000 cases of cancer have been reported during the three years preceding 1908. Dr. Keatinage reports 297 cases treated in the government hospitals during this time. Cancer has been found among the natives of tropical Africa, and in the various Fiji Islands. In judging, however, of the relative infrequency of cancer in uncivilized countries one must take into consideration the shorter duration of life in these regions. Pitchiford states, on behalf of the Natal Cancer Research Committee, that only 13.7 per cent. of the natives in Natal reach the age of 40 years, while in England and Wales 25.7 per cent. of the population are 40 years old or over.

Most authorities believe that cancer occurs more frequently in the higher classes of society than in the lower.

In fact, statistics from civilized nations and from the higher walks of life show that such is the case. Possibly it may be that such statistics are more accurate for the higher classes of society and the difference indicated only apparent.

In this country cancer appears to be much more infrequent among negroes and Indians than among the white population. In Virginia, South Carolina, North Carolina, and also Georgia, the following table arranged by I. Levin (*Zeitschr. f. Krebsforschung*, 1910, ix, 422) illustrates the ratio:—

Virginia:				
White	1,190,000	397	1 in	3,000
Negro	660,000	136	1 "	5,000
South Carolina:				
White	560,000	147	1 "	4,000
Negro	780,000	144	1 "	5,500
North Carolina:				
White	1,250,000	326	1 "	4,000
Negro	630,000	84	1 "	7,500
Georgia:				
White	1,200,000	290	1 "	4,000
Negro	1,000,000	161	1 "	6,000

[McConnell (*Zeitschr. f. Krebsforschung*, 1908-09, vii, 238) has given the following table, comprising 17,286 cases and showing the location of cancer in the two races:—

Organ.	White.		Colored.	
	Male.	Female.	Male.	Female.
Abdomen	463	631	8	5
Bladder	125	49	4	2
Brain	12	14	1	
Breast	36	1256	2	50
Extremities ..	33	25	3	1
Eye	12	6		
Genitals	48	51	1	1
Head, face,				
neck	521	255	10	5
Kidney	40	47	1	2
Larynx	55	11		
Liver	720	1024	22	18
Lung	30	40	1	2
Mouth, tongue,				
neck	477	133	10	6
Ovaries		76	...	4
Penis	20			
Rectum	271	279	9	15
Stomach	2140	1964	55	61
Testicles	7	1	
Uterus		2164	...	127
Undetermined	1223	2500	27	84

Levin (*Zeitschr. f. Krebsforschung*, 1910, ix, 422) has shown the great rarity of cancer among the American Indians. Among the population of 155,455 Indians there were collected only 29 cases of cancer, which occurred between the ages of 35 and 59 years. The rarity of cancer among the Indians cannot be accounted for by the age factor. Statistics show that the average life of the Indian is much longer than that of the white man. Between the ages of 6 and 89 years there were in the United States, per 1000 of the general Indian population, 207.81 Indians, against 219.12 white individuals. Between the age of 95 and 99 years there were 67.93 Indians, as against 65.28 whites, per 1000 of the total population, and 537 Indians per 1,000,000, as against 51 whites, over 100 years of age.

In contrast to cancer, tuberculosis and diseases of the digestive tract are very frequent among the Indians, while, on the other hand, worry is almost unknown among them. H. H. JANEWAY.]

By actual statistics cancer is very infrequent in Africa and the South Sea Islands, and among the aborigines of Australia. However, the inaccuracy of the statistics, discussed on another page, may account for its rarity in these countries.

Rayburn states that cancer is unknown in Buenos Ayres, yet in the southern portion of the Philippine Islands cases have been reported. In Bobol, in 1902, 11 cases of cancer have been reported. Also cases have been reported in Sibutu, in the extreme southern island of the Philippines. The northern end of this island is twenty miles from North Borneo. In the year 1902, 301 cases of cancer were reported from the whole Philippines. These cases came from every province with the exception of three. All told there were 329,671 deaths during the same year from all causes in the Philippine Islands, but Dudley ("Cancer in the Philippines," *Jour. Amer. Med. Assoc.*, 1, 1908, 1663, from whom

these figures are quoted, states that the number of deaths from cancer could be multiplied by 100, and on this assumption he believes that cancer is more frequent in the Philippines than in the United States. Both of these nations live principally upon a vegetarian diet. The Filipino is not a vegetarian by choice, but by necessity. He lives almost exclusively on rice and starchy tubers, varied with a little fish or other sea food. The vast majority never taste meat, and, if, therefore, cancer is more frequent in the Philippines, a vegetarian diet cannot be considered a reason for the apparent immunity of cancer among the southern, uncivilized races.

Very little evidence exists that cancer originates with special frequency in certain localities or houses. The supposition, however, that it does has given rise to the term cancer district or cancer house.

[A very striking illustration of this character has been furnished by Anton Sticker. He gives information concerning a town whose name he is not permitted to give. He states that in this town there occurred, in the years 1825 to 1865, 10 cases of cancer. All these occurred in two houses in a certain low street where most of the houses had damp cellars. During the next ten years there were 4 cases, 2 of which were on the same street. During the next ten years 7 cancer cases occurred in the same town, 5 of which were on the same street; in the following ten years there were 10 cases, 7 of which were upon this same street, and in the year 1895 21 cases occurred on this street and only 8 cases in the rest of the town. From 1895 to 1905 25 cases occurred, 16 of which were on this street. H. H. JANEWAY.]

It has also been shown by Hislop (*Brit. Med. Jour.*, 1909, 2, 1223) that in New Zealand, where cancer has increased during the last ten years, the disease occurs more frequently according to certain climates of rather defi-

nately described regions, but it could not be demonstrated to depend in any way upon diet or manner of life.

It must be quite evident, therefore, that cancer occurs among all races, and also that it shows no predilection for one race, or for any special localities upon the globe. It is true that epidemics have been reported, particularly along certain rivers, but in the face of the above facts little importance can be attributed to them.

While 659,528 persons died in the Civil War, there were 1,021,513 deaths from cancer alone in the United States between 1900 and 1915. In Porto Rico during 1915 there was one death from cancer every day, and in the city of San Juan last year three deaths every month. Aviles (Bol. de la Asoc. Med. de Puerto Rico, Mar., 1918).

Cancer has formed from 1.09 to 1.35 per cent. of the total mortality of the island since 1912. In the public hospital there have been 151 cases of cancer since its opening in 1909; the growth was inoperable in almost 50 per cent. The uterus was the seat of the malignant disease in over 33 per cent. Del Toro (Bol. de la Asoc. Med. de Puerto Rico, Mar., 1918).

Distribution in the Body.—Of considerable importance from the etiological standpoint is the frequency with which cancer attacks the various tissues or organs of the body, that is, its distribution within the body itself, and, inasmuch as this phase of the subject is so intimately connected with the relative frequency of cancer in the two sexes, many of the tables designating both the sex as well as the portion of the body affected, it will be convenient to discuss both these factors together.

Cancer is unquestionably far more frequent among women than among men. This fact is to be attributed to the large number of cancers which

occur among women in the uterus and breast. There are no corresponding organs among men similarly attacked. The large number of cancers of the stomach help to swell the male proportion, but by no means in a manner peculiar to men.

Buday (Second International Congress on Cancer at Paris, 1910, p. 89) has arranged the following table, which illustrates the greater frequency of cancer among women in all countries:—

	Cases among women.	Cases among men.
United States...1900	171.0	to every 100
Sweden.....1890-98	153.8	" " "
England.....1901-05	147.0	" " "
Italy.....1904	127.8	" " "
Hungary.....1901-04	124.7	" " "
Germany.....1907	123.0	" " "
Austria.....1895-98	121.0	" " "
Switzerland.....1901-06	100.2	" " "

For the United States McConnell (Zeitschr. f. Krebsforschung, Bd. vii, 1908-09, 238) gives the following table illustrating the relative frequency of cancer in the various organs of the body in percentages for every 1000 deaths from cancer:—

	F.	M.	Total.
Abdomen.....	76.9	92.4	82.8
Bladder.....	6.2	25.0	12.5
Brain.....	1.7	2.6	2.0
Breast.....	157.8	7.5	
Eye.....	0.7	2.4	1.3
Genitals.....	6.3	9.6	
Head, face, neck.....	31.1	104.2	59.2
Larynx.....	1.3	10.8	4.9
Lower extremities.....	2.1	3.7	2.7
Lungs.....	5.1	6.1	5.5
Mouth, tongue, throat...	16.8	95.5	46.8
Ovaries.....	9.7		
Penis.....		3.9	
Rectum.....	35.5	59.9	42.9
Stomach.....	244.7	430.6	315.6
Testicle.....		1.6	
Upper extremities.....	1.1	3.3	1.9
Uterus.....	276.8		

The following table shows the frequency with which some of the more important organs are attacked in the two sexes, arranged in the order of frequency with which cancer occurs in them. Undoubtedly the majority of the cancers of the liver are secondary growths. Primary cancer of the liver is comparatively infrequent:—

	Male.
Stomach	430.6
Liver	145.6
Head, face, and neck	104.2
Mouth, tongue, and neck	95.5
Lower body	92.4
Rectum	54.9
	Female.
Uterus	276.2
Stomach	244.7
Breast	157.8
Liver	125.9
Lower body	76.9
Rectum	35.5

The following statistics given by Redlich (Zeitschr. f. Krebsforschung, 1907, vii, 261), Feidchenfeld (I. D., Leipzig, 1901), and Reichelmann (I. D., Rostock, 1902) afford a more accurate estimation of the true distribution of cancer within the body, as it is based upon autopsy material. It shows the total number of cancer cases for each organ coming to autopsy within a certain definite time and the percentage which this number is of the whole:—

Organ.	Redlich.		Feidchenfeld.		Reichelmann.	
Stomach.....	176	35.5	165	32.5	288	40.5
Intestines.....	59	11.9	56	11.0	59	8.3
Rectum.....	31	6.3	27	5.3	26	3.65
Large gut	25	5.0	23	4.3	26	3.65
Intestinal	3	0.6	6	1.2	7	1.0
Esophagus	55	11.1	58	11.4	77	10.8
Gall-passage	33	6.6	26	5.1	47	6.6
Gall-bladder.....	22	4.4	21	4.1	39	5.5
Gall-ducts	7	1.4	4	0.8	8	1.1
Bladder and ducts	4	0.8	1	0.2		
Lung	31	6.3	22	4.3	27	3.8
Uterus.....	30	6.0	45	8.9	86	12.1
Uterus and vagina	11	1.4	7	1.4	14	1.9
Ovaries.....	7	2.2	12	2.4	5	0.7
Other genital organs.....	4	2.8	11	2.2		
Vagina.....	2	0.4	7	1.4		
Vulva and vagina.....	1	0.2	4	0.8		
Parovarium.....	1	0.2				
Breast.....	27	5.4	32	6.3	30	4.2
Pharynx.....	11	2.2	4	0.8	4	0.6
Pancreas	9	1.8	13	2.6	19	2.6
Kidney	8	1.6	4	0.8	2	0.3
Skin, esp. face.....	7	1.4	4	0.8	8	1.1
Liver.....	5	1.0	7	1.4	3	0.4
Bladder	4	0.8	7	1.4	6	0.8
Lip	3	0.6	1	0.2		
Thyroid.....	3	0.6	1	0.2	5	0.7
Prostate.....	2	0.4	2	0.4	2	0.3
Nose, pharyngonasal....	2	0.4				
Penis.....	1	0.2	1	0.2	2	0.3
Lower jaw	1	0.2			1	0.15
Tongue.....	1	0.2	6	1.2	7	0.9
Larynx.....	1	0.2	3	0.6	7	0.9
Trachea.....	1	0.2	2	0.2		
Ureter.....	1	0.2				
Questionable	3	0.6	3	0.6	2	0.3

The same table arranged according to the frequency among the two sexes is shown below and on following page.

	Male.	Female.	Total.
Redlich	283	213	496
Feidchenfeld.....	253	254	507
Reichelmann.....	362	349	711

	Redlich.				Feldchenfeld.				Riechelmann.			
	Male.		Female.		Male.		Female.		Male.		Female.	
Stomach	113	39.9	63	29.6	101	39.9	69	25.2	169	46.6	119	34.1
Esophagus	49	17.3	6	2.8	54	21.3	4	1.6	72	20.0	5	1.4
Lungs	26	9.2	5	2.3	20	7.9	2	0.8	21	5.9	6	1.8
Rectum	19	6.7	12	5.6	13	5.1	14	5.5	18	5.1	8	2.3
S. intestine	12	4.2	13	6.1	11	4.3	11	4.3	13	3.7	13	3.9
Pharynx	11	3.9			3	1.2			2	0.6		
Gall-passage	10	3.5	23	10.8	3	1.2	23	9.1	14	3.9	33	9.5
Pancreas	7	2.5	2	0.9	7	2.8	6	2.4	11	3.1	8	2.3
Kidney	6	2.1	2	0.9			4	1.6	2	0.6		
Skin	5	1.7	2	0.9	3	1.2			6	1.7		
Bladder	4	1.4			5	2.0	1	0.4	3	0.8	2	0.6
Liver	3	1.1	2	0.9	5	2.2	2	0.8	1	0.3	2	0.6
Prostate	2	0.7			2	0.8			2	0.6		
Thyroid	2	0.7	1	0.47	1	0.4			1	0.3	4	1.2
Hip	2	0.7	1	0.47	1	0.4					4	1.2
Nose-space	2	0.7										
Duodenum	1	0.35	2	0.9	3	1.2	3	1.2	2	0.6	2	0.6
Breast	1	0.35	26	12.2	3	1.2	32	12.6	2	0.6	29	8.3
Penis	1	0.35			1	0.4			2	0.6		
Vagina and vulva ...	1	0.35	3	0.56			11	4.4			5	1.4
Lower jaw	1	0.35							1	0.3		
Tongue	1	0.35			5	2.0			4	1.2		
Larynx	1	0.35			3	1.2			7	2.0		
Questionable	3	1.1			2	0.8			1	0.3	1	0.3

Influence of Age.—Cancer shows a very definite predilection for certain ages. The majority of cases of cancer occur between 50 and 60 years of age. The following table gives the average age for the development of cancer in the countries mentioned:—

	Years.
Holland	60.5
Denmark	59
Sweden	57
Germany	52.5
United States	52.2
France	50
Austria	48
Japan	47
Hungary	46.5
Portugal	37

Redlich gives the average age for men as 56.4 and women 55.5. He gives the following table for 367 cases:—

	Female.	Male.	Total.
10 to 20		1	1
21 " 30	4	6	10
31 " 40	18	18	36
41 " 50	93	59	152
61 " 70	76	43	119
71 " 80	22	26	48
81 " 100	1	..	1
			367

Cancer is very rare among children, yet Phillips and Lindermann (Zeitschr. f. Krebsforschung, 1908-09, vii, 682) have given statistics of a considerable number of cases in early childhood. Phillips reported 5 cases of epithelioma of the skin in children from 8 to 12 years of age, aside from numerous other cases of new growths of the lymphatic glands in which it was impossible to distinguish between carcinoma and sarcoma.

Carcinoma of the lung has been reported in a boy 5½ years of age. Epithelioma of the larynx has been reported in a child 10 years of age. There have been reported 22 cases of medullary cancer of bones in children from 8 months to 15 years of age; 5 true cases of carcinoma of the adrenals in children from 11 months to 12 years of age.

Pancreatic sarcoma has been reported in 3 children 6 months, 2 years, and 13 years of age. There have been reported

11 cases of carcinoma of the liver in children between the ages of 1 year and 14 years. No case of cancer of the esophagus has ever been reported in children. Cancer of the stomach has been reported in a child 5 weeks old, in a girl 13 years old, and in a boy 14 years old. Primary cancer of the intestinal canal is the most frequent form of cancer in children. There have been reported 37 cases, of which 26 are certain. The age of these vary between $1\frac{1}{2}$ to 15 years. The majority have been between 12 and 15 years of age. At least 11 cases of cancer of the rectum have been reported in children between 11 and 15 years of age. Cancer of the kidney is most frequent in early childhood; besides various forms of medullary sarcoma there occur adenocarcinoma, alveolar carcinoma, and hypernephroma. But if the sharpest criticism is applied there is only 1 case in which the diagnosis is positive; this is one of Perthe's cases, in a boy 9 years of age who had a true adenocarcinoma of the kidney. Twenty-one cases of cancer of the ovary in children have been reported; the ages have varied between 11 and 15 years. All told Phillips has reported 390 cases, and states that 87 of these stood a severe diagnostic test. Epithelial cancer occurs but rarely in childhood. Its greatest frequency is at puberty, and the organs most affected are the skin, intestinal tract, and ovaries. There appears to be no essential predilection for cancer occurring in childhood for one sex more than for the other.

Hereditary Influences.—Much discussion has been indulged in upon the part played by hereditary influences in the development of cancer.

Cullen has reported cancer of the

uterus occurring in three sisters, and believes that hereditary influences bear an important part in the etiology of such cases. Paget maintains that cancer more frequently occurs in the antecedents of cancer patients than in others. Among 2389 women with cancer reported by Pierson from the Middlesex Hospital in London, 359 had family histories of cancer, while of the antecedents of 753 non-cancer cases only 120 were affected with cancer. This shows that cancer seems to be no more frequent in the families of patients with cancer than among those without it. Guillot has found a history of cancer in 11 per cent. of antecedents of non-cancerous patients and in 17.4 per cent. of the antecedents of cancer patients, and he estimates that the incidence of cancer in the parents of non-cancer cases is 16 per cent., as against 17 per cent. of the parents of cancer patients.

The famous case of Madam Z., reported by LeDoux Lebarde, furnishes striking support to believers in the influence of hereditary factors in causation of cancer. There were 15 of the descendants of this woman who had cancer out of 26 offspring, 1 of 7 males and 14 of 19 females.

[It is a well-known fact that the offspring of certain gray stallions develop melanosarcoma with especial frequency. Xeroderma pigmentosum is prone to occur in members of the same family.

Tyzzier (*Jour. Amer. Med. Assoc.*, 1910, iv, 1535, and *Jour. Med. Res.*, 1907, xvii, 155) has shown that, of the offspring of a certain female mouse with a tumor of the lung, 65 attained the age of 6 months, and, of these 65 mice, 20, or 32 per cent., presented tumors, 17 of the same type as the parent.

Bashford (*Lancet*, Nov. 21, 1908) has shown that among human beings in England there is no conclusive evidence that

heredity plays a part in the causation of cancer.

Among men aged over 35, cancer occurs in 1 out of 11. Among women over this age, 1 out of 8 dies of the disease. Therefore, few families escape, and it is difficult to form a correct idea as to hereditary influences. Of 2932 cases reported by Bashford only 669 were available for statistics from the hereditary standpoint; 358 of the latter were without relatives who had had cancer, while 311 had such relatives. These 311 individuals had 359 relatives who had cancer, and among the 359 relatives there were 58 fathers and 114 mothers; 58 bear a ratio of 1:11.5 to 669, or the total number of cases available for hereditary statistics, and 114 bear the ratio of 1:6. These ratios correspond to the normal frequency of cancer.

In the "Fourth Scientific Report of the Imperial Cancer Research Fund," Bashford states:—

"Precise evidence is advanced of the existence of a hereditary predisposition to the development of spontaneous cancer." "It is apparently of the nature of the predisposition of certain tissues to pass into cancerous proliferation, and is not effective by determining an increased suitability of the animals primarily affected for the growth of cancer, as has been tested by transplantation." "While at present it is not possible to explain how the hereditary liability to the development of spontaneous cancer is transmitted, it can be assured with certainty that it does not consist in the inheritance of a soil more suitable for the growth in general." "It can only be inferred with some probability that it is a local or circumscribed tissue predisposition, in virtue of which the mammary tissue is prone to pass from mere proliferative reaction into continuous or cancerous proliferation."

"There is a considerable amount of evidence to show that the predisposition is not a general one affecting the entire body equally, but that the tendency transmitted affects mainly one organ system, so that groups of animals may ultimately be obtained in which different organ systems will present a definite predisposition, other organs of the body not being unduly liable to the development of the disease." H. H. JANEWAY.]

Levin (*Zeitschr. f. Krebsforschung*, 1912, xi, 547) has attempted to study the influence of heredity on cancer from a somewhat different standpoint, and has arrived at rather novel conclusions. The latter are: (1) that resistance to cancer is a dominant character whose absence creates the susceptibility to cancer; (2) that the susceptibility is specific in different families for different organs. He considers that the conclusions to which he came in a previous study (*Annals of Surg.*, 1910, li, 768), that hereditary disposition has no influence on cancer, may have to be revised. Both Bashford and Levin therefore have changed their attitude, and Tyzzier has advanced evidence in favor of the hereditary influence on the causation of cancer.

Exciting Cause.—Of all the factors related to the causation of cancer the most important is, undoubtedly, the question of the existence of a possible exciting cause of its growth.

For a long time a relation between trauma and cancer has been recognized by many. In this country Phelps (*Annals of Surg.*, 1910, li, 609) maintains that there is no connection between trauma and cancer.

Of 115 authors whom he has consulted only 7 have admitted a connection between trauma and the occurrence of carcinoma; 27 limit such a connection to trauma in the form of persistent irritation; 37 to trauma limited to some form of chronic inflammation; 11 have excluded all forms of trauma as having any etiological connection with carcinoma; 12 have admitted the connection of an undefined trauma with cancer; 10 make no mention, however, of trauma as an etiological factor; 9 mention exclu-

sively intrinsic factors in discussing the cause of cancer, and 2 confess ignorance of the etiology of cancer.

[Phelps has made an extensive review of the literature upon this subject and finds that there were 3000 books and articles written upon the connection of trauma and the development of cancer, but, notwithstanding his extensive study, he believes there are only 3 cases in which the connection of the trauma in development of the cancer is sufficiently intimate to allow of a connection between the two. In 2 of these instances cysts seem to have been present associated with the carcinomatous deposits, and the history of the third case merely states that an elderly lady was struck on the back by a tennis ball and where the ball struck her there formed a large and rapid-growing carcinoma.

There seems to have been no microscopic examination made in this case, and Phelps concluded, therefore, that the evidence of a relation between trauma and the development of cancer is insufficient. H. H. JANEWAY.]

The author, however, is inclined to agree with Coley (*Annals of Surg.*, 1911, liii, 449) and considers that there is an etiological connection between trauma, at least in its broadest sense, and cancer. Coley states that in 9 of 46 cases of sarcoma which he has previously reported the tumor developed within one week after the injury and at the exact site of the injury. Since this report he has observed 800 cases, making a total of 970 cases of malignant disease. Of the 970 cases a definite history of trauma existed 225 times, or in 23 per cent. In 117 of the 225 cases, or in 52 per cent., the tumor developed within one month after the injury. Coley also has observed carcinoma of the breast following injury within one week's time in 5 cases; two weeks to a month's time in 14, one month to two months' time in 3, two months to six months' time in 8, six months to twelve months' time in 7,

one year to two years' time in 5, two years to three years' time in 3, and over three years' time in 7, cases.

Unquestionably the closest relation has existed between injury and the development of certain melanotic sarcomas from pigmented moles. Of 250 cases of carcinoma personally observed by Coley there was a history of antecedent trauma in 82, or 32.8 per cent.; 120 of these were carcinomas of the breast.

McWilliams has reported 100 cases of carcinoma of the breast, of which 29, or 44.6 per cent., had a distinct history of antecedent trauma.

Segond has formulated a law that, in order to have a knowledge of the relationship between trauma and carcinoma scientifically acceptable, there should be evidence of a medical examination prior to the injury. In 4 of Coley's sarcoma cases such evidence existed. Coley has also observed 3 striking cases of internal cancer. In cases of sarcoma Sands states that there should probably be an interval of three weeks to one year, and in carcinoma an interval of six weeks to one year between the time of the receipt of the injury and the development of the new growth.

Coley's conclusions are that a local trauma of any kind, from chronic irritation to a single contusion, is frequently the exciting cause of malignant tumors of all types. That a single local injury may be the cause of a carcinoma or a sarcoma is, no longer questioned. This relation in no way depends upon our ability to offer an explanation of the same, nor on the acceptance of any one of the various hypotheses as to the etiology of cancer.

[Ziegler (*Münch. med. Woch.*, 1895, xlii, 621) gives 170 cases of carcinoma, of which

37, or 22 per cent., had a history of trauma. In 171 cases of sarcoma 35 were associated with a single trauma. He reports on 750 collected cases and 50 observed at the Pathological Institute of Munich. In 358, or 44.7 per cent., of these cases cancer was associated with trauma, and in 316, or 39.5 per cent., of the cases sarcoma was associated with trauma. The time varied from almost at once to forty-nine years.

Wilson and Willis (Jour. Amer. Med. Assoc., 1910, lv, 921) reported that 167 carcinomata of the lip, 46 of the mouth and tongue, 2 of the esophagus, 189 of the stomach, 15 of the gall-bladder, 22 of the appendix, 20 of the colon, 42 of the large gut, 57 of the rectum were subjected to microscopic examination for information as to the starting point of the growth. Evidence of the previous existence of a chronic inflammatory process was found in 30 per cent. of the lip cases, 67 per cent. of the stomach cases, 33 per cent. of the gall-bladder cases, 100 per cent. of the appendix cases, 10 per cent. of the colon cases, 40 per cent. of the large-gut cases, and 3 per cent. of the rectum cases. H. H. JANEWAY.]

Häberfeld (Zeitschr. f. Krebsforschung, 1908, vii, 190) discusses the question of the connection between chronic inflammation of the stomach, gall-bladder, and lungs. He bases his statement for the stomach upon autopsies of 662 cases of gastric cancer; 106, or 16 per cent., were found in which, as far as microscopic appearances showed, the disease originated from ulcer. Häberlein considers that 7 per cent. of ulcers of the stomach undergo malignant transformation, while the Mayo clinic believes that there is evidence, in the microscopic sections of 70 per cent. of gastric cancers, that the latter have originated in ulcer. Häberfeld found stones 119 times in 164 primary cancers of the biliary passages. Evidence of the relation of chronic irritation to cancer of the lung is less striking. Three cases have

been reported in which primary cancer of the lung was associated with tuberculosis.

Vaseline employed as a vehicle for drugs such as camphor in subcutaneous or intramuscular injection, is capable of giving rise to serious tumors in the tissues. In 7 such cases witnessed the tumors developed where injections of camphorated oil had been made, and only after an interval of about 5 months to 2 years. There is no spontaneous retrogression. The tumors do not modify the general condition but appear to have a marked tendency to recurrence and give rise to metastases. The authors term these tumors vaserinomata. In the 7 cases reported the tumors were removed, but in all cases recurred. A wide resection, as in a malignant tumor, appears to be necessary. Jacob and Fauré-Fremiet (Rev. de chir., liii, 221, 1917).

Tar and mineral oils, when in contact with the skin, tend to occlude the orifices of the skin glands. This may be followed by irritative follicular or ostiofollicular lesions of the acne type, and may result in multiple flattened or exuberant horny formations, at times like cornu cutaneum. These tumors are for the most part benign, remain small, and may ulcerate, later healing spontaneously. Some, however, pass into large ulcers and require surgical treatment; they may even become generalized and cause death. The lesions develop particularly on the forearms and face. They may, however, occur on the covered parts, exposed to accidental contact of the noxious materials. The condition occurs only in workers who have been exposed a number of years. Lack of cleanliness is a favoring influence. Proper care of the skin is the main factor of safety. G. Thibierge (Bull. de l'Acad. de méd., Aug. 20, 1918).

Investigation of coal, tar, pitch, soot, naphthalene, etc., aniline dyes, petroleum, grease, tobacco, betel nut, Röntgen rays and radium rays, arsenic

and manure as causes of cancer. The investigation showed that mechanical injury *per se* can play only a minor part in the predisposition to occupational cancer. All the agents seem to bring about the predisposition to malignancy in a somewhat similar manner, viz., by becoming impacted in the tissues, where, by giving rise to cell proliferation, they produce a warty condition, then a sore with epitheliomatous margins.

All of the active commodities examined were products of, or are derived from, the products of the death and decomposition of living matter. Carcinoma seems more frequent, in general, at sites continually subjected to organic matter undergoing bacterial decomposition, such as the rectum, stomach and intestinal tract, mouth, uterine cervix, breast, prepuce, anus, scrotum, etc. Decaying organic matter of all descriptions fertilizes living matter, and promotes cell proliferation. Probably the mischievous agents are organic nitrogenous substances of a group common to all the dangerous commodities. The name auxetics is given to these cell-division-producing agents. The predisposition to cancer during senescence may be due to auxetics physiologically free in the tissues. In occupational cancer, in addition to the auxetics produced by mechanical or chemical trauma, there are also those contained in the commodities themselves. H. C. Ross (Jour. Cancer Research, Oct., 1918).

Review of the papers of Fibiger, Stahr, and Yamagiwa and Ichikawa, all of whom claimed to have produced malignant tumors artificially in animals. The lesions reported could be produced as readily in young as in old animals. Again, these reported tumors apparently do not possess the power of continuous growth upon transplantation into animals of the same species. The writers themselves performed experiments on rats and rabbits in which chemical and mechanical irritants were employed, e.g., spine balls in the stomach, injec-

tions of Scharlach R and pine tar into the stomach after gastrotomy, etc. By simple mechanical injury papillary and polypoid tumors, papillary ulcers of the squamous portion of the stomach, and lesions of the glandular portion suggesting cystadenomata, were easily produced. Repeated injections of Scharlach R into the skin of the buttocks caused lesions indistinguishable morphologically from human epithelioma. The work shows that great care should be exercised before reports of the production of cancer by artificial means are accepted. If growth does not continue after the action of the irritant has ceased the tumors should not be considered malignant. Age, organ specificity, and congenital defects play an important part in the origin of the tumor, and irritation alone is an insufficient factor. Bullock and Rohdenburg (Jour. Cancer Research, July, 1918).

Of greater significance still, in its relation to the exciting cause, is the difference in the frequency with which various portions of the body are affected among different races. In England and Wales, out of 10,000 deaths from cancer, there were, among the males, 926 due to cancer of the lip, tongue, or buccal cavity, and 148 due to cancer of the penis and testicles. There were among females 2259 due to cancer of the uterus, 1656 due to cancer of the breast, and 83 due to cancer of lip, tongue, or cheek.

In the whole of India, among 10,000 deaths from cancer among males in the English hospitals, cancer of the penis and testicles was twice as frequent as in England, and cancer of the lip was three times as frequent. Among the females, cancer of the uterus was one-half as frequent as in England. Cancer of the breast was observed three times as often, while

cancer of the lip was four times as frequent.

The fact which we are attempting to develop becomes still more evident when we compare the frequency of the various forms of cancer among the natives of India with its frequency among the English residents living beside them. Cancer of the penis and testicles is ten times as frequent among the Indians, while cancer of the lip, cheek, and tongue occurs about in the same proportion. Among females the frequency of cancer of the uterus and breast does not show any great difference between the two races. On the other hand, cancer of the lip and tongue among Indian women is six times as frequent as among the English women.

The significance of these facts is very great. The excessive frequency of cancer within the mouth among Indian and Ceylonese women is accounted for by the irritation produced by the chewing of betelnut, just as the striking contrast between cancer of the lip, tongue, and cheek in English men and women is directly due to the use of tobacco by the former. The greater frequency of cancer of the penis and testicles among Indian men as compared to the English is undoubtedly due to their uncleanly habits and the absence of circumcision. This is made still more evident by the almost entire absence of cancer of the penis among the circumcised Moham-medans, who have lived for generations close together with the other inhabitants of India. Another fact of importance is the great frequency of cancer of the abdominal wall among the natives of Kashmir, while cancer occurring in this locality is almost unheard of among Europeans. The explanation is found in the fact that in Kashmir the natives irritate the

abdominal wall by wearing upon it a charcoal oven, and the irritation thus produced is responsible for the cancer in this unusual locality.

These facts are important because we may almost say that in them we have control experiments, demonstrating the direct connection between chronic irritation and the incidence of cancer. Less marked evidence of the same facts, but still of very great importance, is the frequency with which cancer of the stomach is preceded by ulcer; cancer of the biliary passages by the history of chronic cholelithiasis; cancer of the breast by mastitis, and cancer of the cervix uteri by the history of cervical laceration and erosions; also the association of bilharzia hæmatobia with cancer of the urinary tract, and the frequent implantation of cancer upon tuberculous and syphilitic processes.

While no definite opinion as to the nature of cancer can be found from these data, they demonstrate at least that no one etiological factor is constantly associated with the disease, but that a great variety of conditions precede it, and such evidence points to the conclusion that cancer is to be considered as a pathological disturbance of the normal cell life. This view will be more fully elaborated.

Influence of Occupation.—Very few statistics upon this subject are available. Those of McConnell (*Zeitschr. f. Krebsforschung*, 1908-09, vii, 238) will serve our purpose as well as any.

For each 100,000 of population according to occupation:—

	For male.
Students, professors, etc.	51.7
Clergymen	102.2
Lawyers	52.5
Physicians	67.5
Office help	37.3
Bookkeepers and correspondents	28.0

	For male.
Bank officials	41.4
Cashiers, auctioneers' agents	58.1
Merchants and storekeepers	52.0
Merchants and storemen	81.3
Dealers and peddlers	62.7
Hotel men	35.3
Hotel and pension officials	60.1
Café and restaurant keepers	28.0
Public servants, police and military ...	42.9
Porters	66.7
Police, nightwatchers, and detectives ...	60.3
Working and serving class	66.5
Laborers	126.6
Men servants	44.3
Manufacturers and mechanical industries	53.3
Bakers and chefs	51.0
Smiths	107.3
Upholsterers	72.6
Iron and steel workers	31.5
Machinists	52.2
Masons and stonecutters	98.0
Weavers	34.5
Painters	45.0
Tailors	58.4
Country occupations, transport and other occupations in open air	69.2
Carters, thrashers, guides	22.6
Builders, planters, and country laborers	87.7
Gardeners and florists	72.9
Stablemen	46.1
Mountain dwellers and quarrymen ...	33.4
Sailors and fishermen	113.1
	For female.
Teachers	47.8
Bookkeepers and accountants	15.1
Washwomen	25.3
Nurses and midwives	105.0
Servants	99.6
Workers in various textiles	9.9
Woman tailors and dressmakers	38.4

The table is given for what it may be worth, but in drawing conclusions from it one must make allowances for inaccuracies incidental to data of this character.

Very little may be said upon the relationship of diet to cancer. No one form of diet has ever been found to influence the progress of the disease in the slightest degree. In general, it is assumed that those living upon a vegetarian diet are to some degree immune from cancer. This view is based entirely upon the supposed infrequency of cancer in China, Africa, and southern countries in which a vege-

tarian diet is more universal. In discussing the geographical distribution of cancer we have shown that other factors should influence our conclusions in this matter. In general, the whole subject, particularly in our present state of ignorance upon cancer metabolism, rests upon a too uncertain basis to permit of even general deductions.

THE ESSENTIAL NATURE OF CANCER.—Of the various theories which attempt to explain the nature of cancer, the parasitic theory is entitled to discussion first. Aside from a number of clinicians who have not extensively familiarized themselves with the pathology of cancer, and a comparatively few pathologists, the parasitic theory has few advocates. Many features of the disease are dissimilar from the known forms of infectious maladies, and, notwithstanding the most painstaking search through a period of many years, no single parasite has ever been definitely demonstrated, although the list of observers claiming to have discovered a parasite is a long one. In estimating the importance of the supposed parasites we may first state that none of them have been constantly found, nor fully confirmed, by other observers. Most of the supposed protozoön forms owe their existence to the innumerable products of intracellular degeneration. The various conditions under which tumor material has been transplanted almost positively exclude the presence of parasites within them. Tumor-cells will withstand exposure to solutions of bichloride of mercury and cyanide of potassium to a degree that any known pathological bacterium or spirocheta cannot endure. No well-authenticated cases of the transfer of a malignant tumor from one human being to another exist. The

few instances of such a nature which are quoted are not beyond criticism, and are so few in number that there is no support for the parasitic theory from this standpoint.

The clinical course of cancer is, also, strong evidence against the parasitic hypothesis. Its spontaneous development from normal tissue; the multiplicity of the forms of chronic inflammatory processes which bear an etiological relation to it; the formation and growth of metastases, and the different character of the immunity in cancer among the lower animals from the immunity occurring in any known form of infection, all strongly indicate that cancer is not caused by a specific pathogenic organism.

Regarding the spontaneous development of cancer from normal tissue, the transition from the normal skin-cells into tumor-cells in some of the earliest growths, particularly in minute cutaneous epitheliomata, is so gradual, and the absence of any chronic inflammatory process is so manifest, that the direct derivation of the young tumor from the normal cells by a primary metaplasia of latter seems clear. The great variety of chronic inflammatory processes which may precede cancer demonstrates that no one specific form of inflammation is connected with its development, such as we would expect if cancer was dependent upon a specific form of parasite.

The formation of metastases always occurs by the sweeping away in the blood-stream of minute particles of tumor-tissue and the subsequent lodging of these in some distant portion of the body, where growth is really the result of an implantation. The surrounding cells, even when of the same nature as those in which the tumor has originated,

do not always participate in the process; we should certainly expect such a participation were cancer due to a parasitic organism. To accept a cancer parasite one must consider it capable of transforming normal epithelial cells into cancer-cells, and then incapable of causing a similar transformation in similar cells, after being carried elsewhere in metastatic emboli.

A degree of protection against the inoculation of cancer can be established among the lower animals, but the character of this immunity is very different from that belonging to any form of infection depending on pathogenic organisms. For instance, animals in which tumors are already growing can be inoculated, though animals in which tumors have retrogressed possess immunity. Animals displaying a marked degree of natural immunity to the inoculation of virulent tumors may spontaneously develop tumors. The products of the disease do not uniformly confer immunity.

Turning now from the parasitic theory to the autogenetic theory, one finds a conception which is still far from complete, but which, in its main outlines, presents a far more satisfactory explanation of the facts surrounding the development of malignant disease. The theory has developed into somewhat different forms according to the stress laid upon two conceptions.

In 1865 Thiersch developed the idea of the difference in the length of life of the various tissues, and the effect upon one tissue of a disturbance in its relation to another. He maintained that the "rarefaction," to use his own word, of the connective-tissue stroma is responsible for the growth of cancer. His book is really the foundation of the autogenetic theory.

In 1877 Cohnheim described the existence within the tissues of isolated groups of embryonic cells, upon the discovery of which he elaborated the theory which bears his name. The hypothesis is briefly as follows: During the period of fetal development, groups of cells become inclosed as isolated islands, within tissues which are different in kind from those into which these cells should have normally developed; at some time later in life cancer develops from these isolated groups.

This theory is a most satisfactory one from many standpoints. Pathologically, the early stages of cancer consist in the proliferation of cells within a tissue to which they do not normally belong. The Cohnheim theory supplies in the earliest stages not only the presence of isolated groups of cells in tissue of a different kind, but also the presence of a cell which has been set apart during embryological development. It requires only a small amount of imagination to suppose that such a cell is endowed with greater proliferative powers. Borrmann, from a study of 286 cases of young epitheliomata, concludes that all the complicated conditions necessary to explain the existence of groups of cells capable of unrestrained proliferation are fulfilled by the assumption of an embryonal inclusion. Borrmann may be said to represent the Cohnheim theory as it is.

The most important fact upon which Borrmann bases his conclusions is: the discovery of some epitheliomata entirely buried within the corium and presenting no connection with any epithelial structure. Mackwald, Tanberg, and Veit have described similar growths; the author has met with two examples which strongly suggest such an origin, though at one point

in each tumor there was a small connection with the epidermis. Further support is derived for the Cohnheim theory by the large class of teratoma, and by those teratomata in which the epithelial portions have undergone malignant change. The wide distribution of chorioepitheliomata, even occurring in the male, furnishes evidence in support of the Cohnheim theory which can hardly be refuted.

To the minds of many, however, the Cohnheim theory does not furnish all that is needed to explain the origin of some cancers. The large amount of clinical evidence on the etiology of cancer above referred to; the possibilities of tissue metaplasia, and the very direct outgrowth of some cancers from the normal epithelial tissue, all point to other factors.

The facts relating to the inflammatory conditions preceding cancer, which Bashford has recorded, have demonstrated to him "that the different forms of irritation, although they have nothing in common, are of more moment than the sites in which they are applied, and are more or less out of accord with the hypothesis of a congenital origin as an explanation of all forms of cancer." Hansemann, Lubarsch and Benecke, and Krompecher have done much to develop the idea of cell metaplasia, and the important part which the epithelial cell itself plays in the development of cancer.

The view of Ribbert is deserving of special mention, as he undoubtedly represents the most careful thought on cancer problems. He combines in a finished theory the essential ideas of Cohnheim and Thiersch, and his hypothesis may be stated as follows:—

The essential cause leading to the development of cancer is an inflamma-

tory process surrounding the proliferating areas. By the products of such a process the epithelial cells become separated from each other, and from the single tissue of which they form a part; they then begin their unrestrained proliferation. In the majority of cases, however, it is an isolated complex of embryonal cells which is so acted upon by the chronic inflammatory process.

From a detailed study which the author made upon the early stages of epithelioma, he cannot believe that the idea of either Ribbert or that of Borrmann include all the factors demanded in the origin of cancer. The histological pictures and the clinical history of the lesions presented in the paper referred to demonstrate that the laws controlling the life growth and metaplasia of the normal epithelial cells themselves include, in many cases, all that may be needed for their transition into cancer. The conclusion in this paper was that the transition into cancer must be regarded as of the nature of a degeneration, in virtue of which excessive proliferative powers replace normal physiological functions and that this degeneration is dependent at times upon the existence of previously isolated cell-complexes, at times upon inflammatory processes of the surrounding connective-tissue stroma, and, what is of more importance, at times upon no discoverable lesion external to the epithelial cells undergoing the transition into cancer. In cases of this last category the individuality of the cells of the organism is without doubt a determining factor.

One of the most constant conditions present in all cases is sepsis of the throat from the presence of carious teeth, pyorrhea alveolaris or septic gingivitis. The normal reaction of

the mouth fluids is alkaline, but in the presence of these septic conditions it is acid. The increased irritating effects of such acid fluids on the mucous covering of the throat is considerable, and may well prove a contributory factor to cancer of the throat. Nearly 96 per cent. of the cases investigated by the writer has occurred in men, and in nearly every instance the patient has used tobacco to excess. Another pernicious influence noted was the baneful but common one of consuming very hot food, and all the cases investigated were found to be people who believed in the free use of common table salt. Salt increases the acidity of the alimentary tract and so causes irritation. Stuart-Low (Pract., Aug., 1917).

Cancer is created in some manner by the division of one cell failing to carry with it the centrosome. The next division leaves it without control as a unicellular type of life capable of lawless growth more or less true to type but without a controlling brain. The cell becomes parasitic, and primarily changes the local field into a slightly acid one as an environment suitable for its growth. Ultimately this fluid permeates the body, a curious cancer cachexia occurs and with it there may be metastases later becoming manifest by growth at any point where cells may be carried. The resistant influence of youth may lie in the rapid reduction and restoration to normal of the acidity. The young cells have not exhausted the protoplasmic control bodies. In old age with hardening of the tissues, it is easier for a centrosome to be immature in its development and it may wholly fail. One-third of the cancers affecting man are found where acidity is constant and high as in the stomach. Cancer occurs but 2 times in the whole length of the alkaline small intestine to 98 times in the large bowel, in which again there is acidity. The same statement may be made concerning the development of

cancer in the urinary bladder, cervix and mouth. The mammary gland, uterus and prostate, subject to carcinoma, are tissues in which degeneration is a normal process and having but a limited period of functional activity. The danger of cancer is increased by all irritation or traumatism which demands a continued cell repair, and is in proportion to that demand. Ultimately exhaustion of cell control bodies occurs, modified by age limitations and chemical surroundings. C. H. Mayo (Can. Pract. and Rev., Nov., 1918).

The writer suggests that cancer cells represent a cellular revolt which ends in the death of both the cells themselves and the tissues in which they proliferate. Slight irritation maintained or a sudden shock is sufficient to cause this revolt only in predisposed tissues. Audrain (*Prog-rès Méd.*, Feb. 22, 1919).

PATHOLOGY.—The exact definition of what constitutes cancer is a matter of some difficulty, for the reason that no sharp dividing line exists between non-malignant and malignant new growths. Many tumors, particularly those of the thyroid glands, are histologically adenomatous and yet follow a most malignant clinical course. Gierke, from his study of animal tumors as well as of human new growths, concludes that no expression of opinion as to the degree of malignancy is possible from the histological structure. Apolant has shown definitely that adenomata of mice can pass into carcinoma and that carcinomata can again pass back into the adenomatous form of tumor.

Mixed tumors of the parotid also furnish illustrations of a form of neoplasm which histologically possesses the structure of a malignant new growth, but clinically amounts to very little more than a benign tumor; after complete

local removal they never return, and after incomplete removal they may return locally, but do not form metastases.

The very interesting tumors known as adamantine epitheliomata also illustrate this fact. In these the histological structure shows every criterion of a malignant new growth, and yet clinically their course is benign. Almost the same statement may be made of many epitheliomata of the skin. Their histological structure is of a most malignant character, and yet their growth may be very slow, and, while they may form metastases, still this occurrence is among the rarest of events.

Similar examples may be found in the many forms of chondrosarcomata; in fact, the gradation between simple chondroma and chondrosarcoma is an insensible one. As has been mentioned, closely related to the failure of a sharp division line between benign and malignant new growths is the question of the transformation of one kind of tumor into another.

There is definite evidence that metaplasia in this sense occurs, but only to a limited degree; certain cystic tumors of the breast have subsequently become carcinomatous, and quite a number of polypoid tumors of the rectum have been reported, upon which epithelioma has arisen at a later date. Whether the so-called carcinomatous degeneration of a myomatous uterus is a metaplasia of this kind is doubtful; in instances of this class what occurs may simply be a growth of carcinoma in the uterine mucous membrane overlying fibromyoma. A fairly large number of cutaneous epitheliomata originating in congenital moles have been observed. Volkman, out of 223 cases of cancer of the extremities, has reported 11 cases of

cutaneous epithelioma beginning as congenital moles. Schafstein recorded that in a series of 989 carcinomata of the breast 23, or 2.3 per cent., developed from previous adenomata. Semon, out of 10,774 miscellaneous cancer cases, reports that 45 grew from benign tumors.

In author's practice there have been a number of undoubted instances of the transformation of benign tumors of the skin into malignant neoplasms. In one patient particularly, there were two small growths on the side of the body, both of which were congenital. One presented the appearance of a simple pedunculated papilloma, while the other, though formerly of a simple character, had lately become larger and ulcerated; on this account it was excised and examined microscopically, and the examination proved it to be a typical basilar-celled epithelioma.

A consideration of these facts makes it clear that the metaplasia of one kind of tumor into another occurs only in rare instances, and then the transformation produces a closely related tumor. Indeed, one may fairly raise the question, in regard to the majority of cases cited as instances of the transformation of benign into malignant neoplasms, whether the malignant tumor does not actually arise "de novo," in the manner suggested in the discussion of uterine fibroids.

The calcification of certain tumors, the formation of cartilage in others, and the changes in form and shape of the different varieties of epithelial cells can all be viewed in the light of various retrogressive changes; similar changes also occur in many other pathological processes. In neither case do they transcend the limit permitted by the biological possibilities of the cells in

which such changes occur. Nevertheless, these possibilities are sufficient to render it impossible to draw a clear-cut line between malignant and benign tumors.

A malignant neoplasm may be defined as one whose cells exhibit a progressive tendency to invade the neighboring tissues, either singly or in masses, and in them there is no true encapsulation.

A benign tumor, on the other hand, is encapsulated, and, while increasing in size as a whole, encroaches upon, rather than invades, the neighboring tissues. Such a criterion as this always makes it possible to place certain of the borderland growths in a correct classification; on the one hand, neoplasms which, although benign, still, on account of their size and sometimes even from their rapidity of growth, are capable of destroying life, and, on the other hand, growths which, although malignant, may run a relatively harmless course, and unless removed with special thoroughness, always recur and are capable of hopelessly destroying the neighboring tissues. This single definition also furnishes a pathological basis for the explanation of all the other characteristics of malignant tumors.

Malignant neoplasms may be divided into those of mesoblastic origin and those of epiplastic origin.

I. The mesoblastic tumors are those which consist of an unrestrained reproduction of a mesoblastic type of cell. They may be further subdivided into:

a. Sarcoma; an unrestrained reproduction of a connective-tissue type of cell.

b. Lymphosarcoma; an unrestrained reproduction of a lymphoid type of cell.

c. Endothelioma; an unrestrained reproduction of an endothelial type of cell.

d. Glioma; an unrestrained reproduction of glia type of cell.

e. Melanoma; an unrestrained reproduction of the chromatophore cells.

II. Malignant tumors of epiblastic origin may be subdivided as follows:—

a. Malignant adenoma; a tumor preserving adenomatous characters, but being to a greater or less degree an unrestrained proliferation of a glandular type of cell.

b. Carcinoma; an unrestrained reproduction of a glandular type of cell.

c. Epithelioma; an unrestrained reproduction of an epithelial type of cell.

A discussion of cancer must include these different kinds of tumors, although the chief interest centers around sarcoma, epithelioma, and carcinoma. All three of these are of frequent occurrence, and together are responsible for about 5 per cent. of the deaths over 35 or 40 years of age.

About 6 per cent. of all patients dying in Bellevue Hospital and coming to autopsy are subjects of malignant disease. Of 298 malignant tumors observed *post mortem* at this hospital, 220, or 74 per cent., were attended by metastases. The lymph nodes, liver, pleura and lungs, bones, and adrenals were the organs most commonly metastasized, and they were involved in the order named. Epithelial tumors predominated over those of connective-tissue origin in the proportion of 8 to 1. The lymph nodes, liver, lungs, pleura, and bone marrow give rise to malignant growths only rarely, but metastasis to these organs is common, while the stomach, breast, pancreas, prostate, etc., frequently give rise to malignant tumors, but are themselves seldom metastasized. D. Symmers (Amer. Jour. Med. Sci., cliv, 225, 1917).

Malignant Tumors of Mesoblastic Origin.—The *sarcomata* are composed

of cells, intercellular substance, and vessels. The cells vary much in size, shape, and number in different tumors. The most typical form is spindle shaped, each end tapering off into a fiber of considerable length. In many tumors these cells are arranged close together in bundles, and are of small size; such a tumor is less malignant. In others the spindle cells are larger and relatively not so long, giving them a plumper appearance and a larger nucleus in the center; these tumors are more malignant. Other sarcomatous tumors are composed of cells which are almost round, or more or less cuboidal and polygonal, owing to pressure of contiguous cells. These tumors are still much more malignant; their cells vary much in size. In the more rapidly growing tumors nuclear division may outstrip the division of the cells, thus giving rise to very large cells with many nuclei (giant-cell sarcoma). In other tumors karyokinetic division may proceed so rapidly that the normal orderly sequence of changes are not preserved. This results in many irregular nuclear figures, and in unequal distribution of the chromatin contents of the daughter-cells. In the more malignant and rapidly growing tumors the intercellular substance is scanty in amount, while in the slower growing forms it is more abundant, and this is particularly true in regard to the spindle-cell sarcomata. The character of the intercellular substance varies greatly. In some forms it may be collagenous and fibrillar; in the latter tumors the fibers form a part of the intercellular substance.

In other sarcomata the intercellular substance is largely composed of mucinogenous substance; when this is present in large amounts such a tumor

is named *myxosarcoma*. In the same manner the *chondrosarcomata* and the *osteosarcomata* are differentiated from each other by the character of the intercellular substance. In still other tumors there may be a combination of an unusual proliferation of the blood-vessels with a true sarcomatous development of the connective-tissue supporting framework. When this is the case we have a mixed tumor formation, and the condition is named *angiosarcoma*.

Sarcomata may occur in any portion of the body. Their favorite sites are the long bones of the extremities or their periosteum; they also frequently occur in the subcutaneous tissue. They are more rare in connection with the internal organs. The kidney and uterus are perhaps more frequently attacked than other organs; they are not uncommon in the testicles and ovaries. They are less frequent in the breast, and occur still more seldom in the other organs.

Deserving of special mention are the *myeloid sarcomata* of the long bones. Histologically these present groups of giant cells separated by a very characteristic spindle cell. The giant cells are not always evenly distributed throughout the tumor, but tend to be collected together in groups; they are very large, often containing as many as 50 to 100 nuclei. Their appearance suggests normal osteoblasts. The formation of new bone in these tumors approximates also the physiological method. An osteoid substance is deposited and along this are arranged the spindle cells, in such a manner that one can attribute to these cells true osteoblastic functions. This approach to the true physiological process is in direct unison with the benign nature of these tumors. Their favorite sites are the gums (malignant epulis)

and the marrow of the long bones, especially of the extremities. A very frequent location is the lower end of the femur. As the tumor grows it presses the shell of bone surrounding it in a peripheral direction, until finally this becomes so thin that it will crepitate on pressure like an eggshell.

In certain vascular tumors an actual pulsation occurs, producing the so-called bony aneurisms. In bones which are the seat of these tumors, spontaneous fractures are most liable to occur.

The *chondrosarcomata* are rarer; when they occur in connection with the internal organs they are often classified as mixed tumors of these organs. Finally there may occur tumors containing both bone and cartilage. Although these usually originate from the periosteum, they may also occur in portions of the body in which this membrane is not present, as the breast or bladder.

Sarcomata increase in size by both invading and pushing aside the surrounding tissue. No tissue is able to resist their progress; the skin ulcerates over them, and bone atrophies and necroses before them. Sooner or later they invade either the blood-vessels or a lymphatic stream in their path, and small particles of tumor-tissue are swept away, to lodge in distant locations. These then grow as metastases and always reproduce the primary tumor in its typical structure in the locations where they lodge. Sarcomata do not often invade the lymphatics, and when they do they rarely pass the glands to which the lymphatic stream leads which drains the region of the primary tumor. This method of metastasizing occurs most often with the softer, round-cell variety of sarcoma; the usual manner of metastasis in sarcoma is through the blood-vessels. The

wall of the vessel is entered, and a small portion of the tumor is carried away, which lodges in the first small-sized vessel or capillary which it meets and through which it is unable to pass. Naturally, therefore, the most frequent location for metastases is the lungs, or the small divisions of the portal system in the liver. For the same reason the terminal vessels of the brain and kidney are frequent stopping places of these metastatic emboli. No portion in the body, however, is exempt, and after death from sarcoma it is not unusual to find many organs in the body affected.

The degree with which the metastases reproduce the primary tumor is of interest. In the osteochondrosarcomata the metastases also contain bone and cartilage, so that the various cells of the tumors retain the capability of forming bone, cartilage, and fibrocellular tissue. In actively proliferating tumors the metastases often exaggerate the more atypical characters of the neoplasm; the cells are less well formed, or the giant cells are more numerous and irregular in appearance. The author is inclined to regard these differences as an expression of the continuation of the metaplasia by virtue of which the primary tumor has come into existence.

A very special and important form of sarcoma, and one which is associated in a peculiar manner with the skin, is *melanoma*. It forms a group of tumors differentiated from other neoplasms by very definite characteristics.

Melanotic tumors may originate in the choroid coat of the eye or in the skin of any portion of the body; a favorite starting point is the outer surface of the lower leg, and the skin in the region of the umbilicus. The primary tumor may exist for years, indeed,

throughout life, without showing any proliferative tendencies; then suddenly, without apparent occasion, or perhaps after an attempted removal, it will begin to grow and almost immediately take upon itself most malignant qualities. These tumors are of very rapid growth, and form very extensive and early metastases, and there is scarcely any neoplasm more malignant. It is not unusual also for the same anomaly to exhibit itself in the metastases which may have remained quiescent for years, and then suddenly grow at a very rapid rate. When cases in which the metastases exhibit such a course occur after the excision of the primary tumor, the clinical history is very unique. The patient may remain well for years, indeed, so long that he or she has entirely forgotten about the removal of the small, discolored wart two, three, or even five years previously. A rapidly growing tumor then develops within the brain or in some other internal organ, and the patient quickly succumbs.

It is from this fact that the error has arisen of supposing that it is a dangerous practice to remove pigmented warts. Often these are not removed until they show some evidence of growth; then metastases have occurred and the patient will succumb from general melanoma in a relatively short time. The common interpretation of such a course of events is that the excision has been responsible for exciting the otherwise harmless mole into a virulently active growth. As a matter of fact the author feels convinced that in these cases metastases had already taken place at the time of excision, and not as a result of it. In this class of cases, there has seldom been any recurrence at the site of the original tumor, if the patient is fortunate enough to have had a proper

excision, and not such incomplete and stimulating forms of treatment as curettage or caustic applications. When recurrence takes place only in distant portions of the body, and not in the site of the primary growth it must be assumed that this latter has been completely removed, and this, therefore, is an argument for the early removal of all pigmented growths, without waiting until they have begun to develop a malignant character.

The pathology of these tumors is as characteristic as their clinical history. They are composed of cells presenting a great variety of forms; often they are definitely epithelioid in shape; at other times fusiform, with a number of branching processes; again they are definitely spindle-shaped, each end being drawn out into a long, slender process. The typical cell of these tumors contains pigment; but many cells, even from darkly colored lesions, are not pigmented, and some typical melanomata contain no pigment. Another peculiarity is that many of the metastases arising from deep-colored growths may be pigment free.

The connection of these tumors with congenital nevi raises an interesting question. Are they in any way related to nevi? The author believes that the term *nevus* is used much too loosely. Two rather definite forms of growths are included under this name. We have, first, vascular nevi, in which the tumor is composed of endothelial cells, forming, in a greater or less perfect manner, walls of small vessels, and, second, we have the congenital, discolored growths, known as pigmented nevi, in which no vessel walls are found, but only cells which on superficial inspection show many similarities to those of vascular nevi. The author

feels that to apply the name *nevi* to these latter tumors is misleading; they form a definite entity by themselves. Many of them may be entirely unpigmented; in many the cells are more or less cuboidal in shape. It is particularly in connection with this latter class that melanoma arises, and a study and comparison of these various growths with themselves, and with melanoma, suggest that these congenital neoplasms are really cell-complexes which have been set aside during the process of development, and, in fact, represent the early stages of true melanoma.

The interesting question next suggests itself, whether we shall consider these melanomata as epithelial tumors or as of connective-tissue origin. Their close relation to epithelial structure, their pigment-forming property, the peculiar shape of many of their cells, particularly in some of the early nevoid forms, suggest to some observers that they must be of epithelial origin. On the other hand, the fact that no direct connection exists between them and the epidermis and the tendency to a fusiform shape of their cells in their most typical form (demonstrated so clearly by Ribbert in teased preparations from choroidal growths) make the term melanotic sarcoma correct for other observers. Ribbert has undoubtedly done the most work on these growths. He believes them to be of connective-tissue origin, and that they represent a special form of pigment-forming connective-tissue cell, to which he applies the name *chromatophore*.

A form of sarcoma which is of very great interest both clinically and pathologically is *lymphosarcoma*. The units composing this tumor are the round

lymphoid cells of the lymphatic glands. With these, larger cells are also present, possessing a relatively greater amount of protoplasm, and resembling the cells of the follicles of the gland. The endothelial elements of the gland also undergo proliferation, and the results of this may at times form considerable portions of the tumor. In other growths, especially those with large amounts of lymphoid cells, the supporting connective tissue and endothelial elements may be present in only small amounts. The changes in the endothelial structures in no way differ from similar changes present in inflammatory processes. In many of them several nuclei may be present, so that giant cells may be of frequent occurrence. Another kind of cell often found in these tumors is the eosinophile cell; it is not always present, but, when it is, it is of diagnostic importance. A fine reticulum supports all these elements, and this varies in amount in an inverse ratio to the other components. It may even to a large extent replace the true elements, and in such cases gives rise to firm, hard tumors.

The locations of preference for lymphosarcomata are the lymph-glands of the neck, axilla, and anterior mediastinum; in the latter region the thymus may form the starting point of the growth. Less frequently they may arise from the palate, tonsils, and lymphatics of the intestinal canal, and still more rarely from the spleen, liver, lungs, or even mamma. The tumors are essentially malignant growths, and their metastases invade every organ.

Another change which is peculiarly associated with these tumors is the collection of lymphocytes within the blood. It is natural to suppose that the tumor elements are easily swept into

the circulation and there collect, producing a relative lymphocytosis. Ribbert even concludes that not only is pseudoleukemia a lymphosarcoma, but also leukemia, and that the latter is simply a later stage of the disorder.

The writer found that inoculated tumors failed to grow when chloroform-toluol, hydrochloric acid, potassa, acetone, mercuric chloride, formaldehyde or iodine was added to the suspension in minute amount. Pentimalli (*Riforma Medica*, Apr. 14, 1917).

The writer was able to cultivate tissue from white rats, spindle-cell sarcoma in blood plasma from the same animal or a hen. The cells grew well for 6 or 7 days but then died off unless transplanted. Renovation of the nutrient medium intensified the proliferation of the cells. The cells may undergo morphologic differentiation until they show the spindle shape. A. H. Roffo (*Prensa Med. Argentina*, Dec. 10, 1917).

Malignant Tumors of Epiblastic Origin.—Under this head must be described a number of tumors whose pathology approaches closely that of simple adenoma, and whose growth is mainly expansive, and, yet, the more rapidly growing of them possess invading qualities and form extensive metastases.

Neoplasms of epithelial origin deserve a separate classification from true carcinomata, for the reason that there is every gradation between their simple benign forms and the malignant varieties; the former are slow-growing, well-localized, and encapsulated adenomata.

The pathology, however, is essentially the same as in the more malignant, progressive, and metastasizing forms, and every intermediate step may be observed between them. They illustrate well the point mentioned that no sharp line of division exists between benign

and malignant tumors. These tumors include cylindroma, which occurs chiefly in the oral cavity, in the palate, on the floor of the mouth, in the region of the salivary glands, in the orbit, or in the accessory nasal sinuses, rarely elsewhere. They are characterized by anastomosing columns of epithelial cells, of varying thickness and configuration. Between these, or within tubes formed by them, dependent partly upon the collection of the secretions of the cells, and partly upon a hyaline degeneration of the stroma, is a clear, more or less homogeneous material, from the tube-like character of which the tumor obtains its name. These tumors are essentially benign; they rarely recur after removal and more rarely still from metastases.

Mixed Malignant Tumors.—For the sake of completeness, mention will be made of the *mixed tumors of the salivary glands*, especially of the parotid; these should never be classed as carcinomatous. They do not form metastases, and when properly removed do not recur. They are composed of columns of cells, sometimes solid, sometimes inclosing spaces or concentric pearls of flattened cells. Such definitely stamp the cellular portions of the tumor as epithelial and not endothelial. The arrangement of these cells is very like that in cylindroma, the only difference being that there is not the extensive amount of the same type of degenerative changes and secretory collection as in the latter. The peculiar feature of the mixed tumors of the salivary glands consists in the great variety of different kinds of mesoblastic tissue between the epithelial portions of the tumors. The epithelial columns may be separated by mucous tissue, by ordinary connective-tissue stroma, by fat,

by cartilage, and even by bone. The locality of the salivary glands, particularly the parotid, is such that it is an easy matter to conceive how developmental abnormalities could cause the deposition of all these varieties of mesoblastic tissue among the lobules. These tumors become malignant even more rarely than the cylindroma, but at times their epithelial portions may burst the capsule, and develop into real carcinoma. They find, therefore, a place in a discussion of malignant growths.

The *adenomata* of the breast, prostate, and kidney may be omitted in this discussion, but adenomata of the adrenal and liver are frequently malignant, and, therefore, deserve special mention. Of particular interest are the adrenal adenomata, otherwise known as *hypernephromata*; the interest centers around the very wide distribution of embryonal complexes of adrenal tissue. Small masses of this tissue occur widely distributed throughout the body; they resemble in every way the adrenal, with the exception that the tubules, when definitely present, are not arranged in an orderly direction, but irregularly anastomose and wind around. These complexes of cells are most frequent in the adrenal and in the tissue about it, or in the kidney. They are also encountered in the broad ligament, in the ependyma, on the under surface of the liver, and in the lesser omentum; also in the ovary and solar plexus. They form a strong argument for the development of tumors from embryonal complexes. When such tumors acquire malignant characters they often attain a very large size, even eight to nine inches in diameter. These tumors often show extensive necrosis in their centers;

although they are very vascular, and interstitial hemorrhages are frequent. They are dangerous, both from their size and the frequency with which they metastasize. Metastases occur oftenest in the liver and lymph-glands, but also in the brain and lungs; the metastases result from the breaking of the capsule of the tumor and the invasion of the surrounding vessels and lymphatics (see ADRENALS, DISEASES OF, vol. i).

Of similar significance are the *adenomata of the liver*. These most frequently occur with cirrhosis of the liver, and originate in multiple locations in that organ. Usually they remain of small size, undoubtedly representing small, regenerated areas; at other times, however, they take on a more extensive growth, and form tumors of the size of a walnut or apple. Not infrequently others become still larger and develop into definitely malignant growths, which then invade the vessels, especially the portal vein or the inferior vena cava, and thus become transplanted to other regions of the body, heart, lungs, bones, and lymph-glands.

The histology of these small tumors closely agrees with that of normal liver-cells; at times solid columns of cells are found; at other times the chains of cells surround lumina in the interior of which are cell detritus and gall-stained coagula. The metastases are often functional; many of them never develop, but frequently retrogress and perish. Ribbert assumes that these tumors grow directly from the liver-cells.

Similar adenomata grow from the *thyroid*; they resemble the thyroid parenchyma, but are easily distinguishable from it, and form metastases which show a predilection for the extremities

of the long bones. Both the metastases and the original tumor are slow-growing and run a very benign course.

The consideration of these adenomata finds a proper place in the discussion of cancer, because those which we have described also occur in forms which are malignant. In the main, however, their growth is slow and expansive, and always so in their early stage. It is this feature of expansive growth that distinguishes them from true cancer. In true carcinoma or epithelioma the increase in size is, from the very start, dependent upon an infiltration of the surrounding tissue by new cells. Yet, after all has been said, the difference between these and the adenomata is only one of degree. Many of the carcinomatous growths must be termed adenocarcinoma, and, as was mentioned above, there is no sharp line between the two types. The writer desires to lay special emphasis upon this fact, as it establishes a closer relation between the normal tissue and carcinomatous tumors.

Carcinoma may occur wherever epithelial tissue is present. The essential element is the invasion of the neighboring tissues by groups of cells which present a greater or less deviation in their appearances from the normal cell. The different forms of these growths depend upon the different relation of these cells to each other and to the connective-tissue stroma, and also to the amount and character of this stroma. In general, the cells of carcinoma simulate the epithelium of the tissue or gland in which they arise. It may thus be adenomatous, or alveolar, or acinous, and at times the epithelial elements are so excessively developed that the tumor seems to be practically solid with cells. Such growths occur in any

glandular organ, but particularly in the breast, gall-bladder, intestines, and lungs.

In other tumors the glandular elements form anastomotic columns of cells, separated by a greater or less amount of stroma. In some slow-growing tumors, particularly of the breast, the cellular elements may also be few in number and separated by much well-organized fibrous tissue. Tumors of this kind are called *scirrhous carcinomata*. In some tumors a single layer of cuboidal or cylindrical cells lines glandular-like spaces. Cylindrical adenocarcinomata of this variety usually occur in the hollow organs, particularly the stomach, colon, or rectum; they also occur in the uterus, gall-bladder, pancreas, lung, prostate, and mamma. Other tumors show a papillary form of growth, with long, slender processes lined with a single layer of cylindrical cells. These occur especially in the bladder or uterus; they have also been described in the digestive tract. Many carcinomata secrete large quantities of mucus; this is especially true of the cylindrical-celled growths. The mucus collects in the interstices between the epithelial portions, producing the macroscopic appearance of a jelly-like substance; such conditions are generally termed mucinogenous degenerations. The analogous colloidal degeneration also occurs, but it is rare.

Epithelioma of the skin follows two main types of growth: the spinous or *squamous-cell epithelioma*, and the *basilar-cell epithelioma*.

The cells of the squamous type resemble those of the prickly cells of the stratum Malpighii; they are large, connected to adjacent cells by spines, and tend to invade the surrounding

connective tissue in large groups. Frequently they are concentrically grouped; by virtue of this, and the continued proliferation, concentric masses of flattened cells result, forming the so-called "pearls." This spinous type is the most malignant form of epithelioma of the skin.

In all forms of malignant tumors of epiblastic origin the formation of secondary growths at a distance from the tumor is of frequent occurrence, though the various varieties of tumors differ in the rapidity and frequency with which such secondary growths form and the sites in which they first locate.

As has been indicated, sarcomatous metastases usually occur by the bloodstream. In carcinoma and epithelioma the cells, at first, almost always are swept away in the lymph-channels. Why it is that the metastases of these two forms of malignant new growths invade the body by means of different paths is not thoroughly understood. It may be due to the fact that a connective-tissue cell more readily forms a part of a vessel-wall than does a carcinoma cell. At any rate carcinoma and epithelioma spread through the lymphatics. The cells of these tumors accomplish this not only by means of the direct extension of growth, but also by ameboid movement of individual cells (Ribbert, "Das Carcinom des Menschen"). In sections of these tumors their cells are seen filling the crevices of the stroma and lymphatic spaces.

By the vessels of the latter the cells are conveyed to the regional glands which, for a time at least, form a barrier to further extension of the growth. The efficiency of this barrier is best appreciated in squamous-cell



Carcinoma of the Uterus. (*Kast.*)

epithelioma, which form of cancer never invades the general body beyond the first set of lymphatic glands.

[The importance of metastases and the frequency of their occurrence with various tumors can be appreciated by the following tables taken from Redlich's article, which shows the frequency with which cancer of various organs metastasize at the time of death:—

	No. of cases.	Cases dying with metastases.	Redlich's percentages.	Feldchenfeld's percentages.
Breast	26	26	100.0	96.2
Pancreas	8	8	100.0	77.0
Lung	30	29	96.6	71.4
Gall-passages....	32	30	93.7	92.3
Kidney	8	7	87.5	
Ovaries, vagina, vulva.....	15	13	86.7	
Stomach	156	131	84.0	85.8
Uterus	34	27	79.5	59.5
Esophagus.....	52	39	75.0	76.8
Pharynx	11	8	72.7	
Large gut	20	14	70.0	53.2
Rectum.....	23	16	69.6	66.7

H. H. JANEWAY.]

In quite a number of instances metastases have involved organs without having attacked the lymph-glands. The frequency of such an anomaly with cancer of the various organs among the cases reported by Redlich is indicated in the following table:—

Stomach	17 times
Gall-passages	10 "
Large gut	4 "
Esophagus, lungs, uterus, breast, kidney	3 "
Ovaries, pancreas, rectum.	2 "

The following tables show the percentages of cases of carcinoma of the various organs which had formed, at the time of death, metastases in the lymph-glands, on the one hand, and in the organs of the body, on the other hand:—

PERCENTAGES OF CARCINOMA OF VARIOUS ORGANS FORMING METASTASES IN THE LYMPHATIC GLANDS.

	Redlich's cases.	Feldchenfeld's cases.
Breast.....?	88.5	92.0
Lung.....	86.6	71.4
Pancreas.....	75.0	61.5
Pharynx.....	72.7	
Stomach.....	72.4	70.3
Uterus and vagina ...	70.6	59.5
Esophagus.....	67.3	73.2
Gall-passages.....	62.5	73.1
Rectum	60.8	50.0
Large gut	50.0	40.0
Kidney	50.0	

PERCENTAGES OF CARCINOMA OF THE VARIOUS ORGANS FORMING METASTASES IN OTHER ORGANS.

	Redlich's cases.	Feldchenfeld's cases.
Pancreas	100.0	69.2
Breast.....	92.3	88.0
Kidney.....	87.5	
Gall-passages.....	81.3	84.6
Lung.....	66.6	52.4
Stomach	65.3	54.1
Vulva	46.6	
Vulvovagina.....	35.3	28.2
Rectum	31.8	50.0
Pharynx.....	27.3	

The second variety of epithelioma of the skin, the basilar type, reproduces cells which strongly resemble the cells of the basilar layer. Many forms of this tumor occur, and various subdivisions have been suggested, depending upon the arrangement of these cells. They have been divided into adenomatous, acinous, or cystic groups. In general, however, they all present the same essential characteristics, and the author sees no reason for subdivision of this class.

The early stages of these tumors consist of simple projections of thickenings of the basilar membrane into the corium. The invasion of the corium

by these cells steadily increases, with the production of many different appearances, which may all be described by stating that the various groups of cells within the corium are of larger or smaller size, and are connected with anastomotic columns of varying thickness and length. When the adenomatous character is more marked, cystic degeneration is frequent. From the occurrence of these cysts the name adenoma sebaceum cystoides has originated. The tumors of the basilar type are all of a relatively benign nature; they are slow of growth, and, with rare exceptions, do not metastasize. Frequently the tumor processes are of great length, and in all of them the epithelial elements are very abundant.

Chemistry of Cancer.—The chemistry of cancer at the present time is in a very unsettled state. As Beebe states, "the chemical study of tumors is in its infancy. We have scarcely proceeded far enough to know where the medical problems are, nor have methods now available been perfected to such an extent as to enable a decisive experiment to be made." "No phase of metabolism," says this investigator, "has been described in cancer which does not have a counterpart in non-cancerous conditions. This applies to such questions as the nutritive relations between the cancer cells and the normal body tissue, to the nitrogenous balance, retention or elimination of sodium chloride, excretion of acetone, the relation of ammonia excretion, and to a possible acidosis. Diet doubtless forms an important part in the growth of cancer, possibly even in the origin of the disease." This view is confirmed by clinical experience and by work upon experimental cancer.

The question of the existence of specific cancer poisons is an important

one. Evidence exists that such toxic substances exist, but no proof that it is effective in causing cancerous cachexia. Beebe says, in this connection, "two questions arise in connection with the presence of ferments in cancer: Are there ferments in cancerous tissue which are peculiar to it? And, second, do any of the ferments present in cancer have any marked heterolytic activity? Some evidence exists which permits of a possible positive answer to both these questions, but at present there also exist conflicting statements."

It is rare for malignant tumors to occur *de novo* in multiple locations. Though rare, there are relatively numerous and well-authenticated references to several varieties of tumors, and various forms of epithelial cancers themselves, occurring independently of each other in different locations of the body. Ribbert ("Das carcinom des menschen") has reported a number of such instances and Pusateri another.

In nearly all cases of cancer and sarcoma examined the author found alkalinity of the serum greater than that of serum of normal individuals. M. L. Menten (Jour. Cancer Research, ii, 179, 1917).

The accelerative action of cholesterol and tethelin, the anterior pituitary active principle, on the growth of carcinoma is dependent on the hydroxyl radical. The writers infer that this is not due to their possession of a hydroxybenzol group, but that the accelerative action of cholesterol is in some way rendered possible by its possession of a hydroxyl group. Robertson and Burnett (Jour. Cancer Research, Jan., 1918).

SYMPTOMATOLOGY.—The symptomatology of cancer depends so greatly upon its location that it cannot be taken up in detail in a review of

this kind, but certain general features may be mentioned.

In the large majority of cases the appearance of a tumor or "lump" is the first feature to attract the attention of the patient; the only exception to this statement relates to growths in the internal organs, and even among these a tumor may be the first symptom noticed by the patient, but more frequently it is a disturbance of the function of the organ affected that first attracts attention. Even in the latter case careful examination by the physician usually reveals a tumor, although instances are constantly occurring in which a malignant growth has not been diagnosed until an autopsy has been performed. Such a condition is more apt to exist when the primary tumor remains small, and the secondary growths far outstrip it in rapidity of growth, or when, from the location of the primary growth, it interferes, even when of small size, with the function of some important organ.

[An illustration of how the first of these conditions may obtain is furnished by a case coming under the observation of the writer. In this case a primary epithelioma of the antrum escaped notice, until only a few weeks before the patient's death, while the metastases in the lymph-nodes, which had been present two years before death, and which had been operated upon two or three times, had been regarded as the primary tumor. H. H. JANEWAY.]

Illustrations of the second class of conditions are furnished by certain cancers occluding the common bile-duct, or the pyloric opening of the stomach, or intestinal lumen, and even diffuse cancer of the whole gastric or intestinal wall, or one involving the head of the pancreas. In neoplasms of the internal organs it is a disturbance of the function of the organ that almost always first calls the attention of both

patient and physician to the disease. For detailed description of such growths the reader is referred to articles on the various organs; it is the scope of the present review to outline in a general way the main features of cancer, but a few illustrations may be given. Thus, in carcinoma of the esophagus the first symptom is dysphagia; in the carcinoma of the stomach there is a disturbance of gastric digestion or symptoms of pyloric obstruction; in malignant disease of the head of the pancreas or bile-duct, obstructive jaundice occurs; in the intestines, there will be chronic intestinal obstruction; in carcinoma of the rectum we have constipation, or bleeding or discharge from the anus. Hemorrhage from carcinoma of many organs often constitutes the first symptom, and this is especially true of carcinoma of the uterus and bladder.

The character of the swelling in internal cancer may or may not give diagnostic information; in many instances it aids materially. There is often present a certain firmness and nodular character to the surface, which belongs to cancer alone. On the other hand, the character of the tumor is of the greatest importance in all external growths, and in those superficial internal growths which are susceptible to direct examination. In describing these it will be necessary to distinguish between sarcoma and carcinoma.

Peripheral sarcomata always first appear beneath the skin, or in direct connection with some bone, either filling its medullary cavity or growing from its periosteum; the tumors may attain considerable size before involving the skin or ulcerating through its surface. The consistency of sarcomata varies greatly, according to the character of their cellular elements. The

osseous system forms a special site of predilection for sarcoma. When growing in the medullary cavity it gradually distends the latter, producing a fusiform swelling around the whole circumference of the bone; as the tumor increases in size the shell of bone around it becomes thinner and thinner, until finally there is a mere crepitating layer of bone, and spontaneous fractures are of frequent occurrence. It is, however, astonishing how large a size these tumors may attain before such an accident occurs.

When sarcoma grows from the periosteum it produces a fusiform swelling on one side of the circumference of the bone to which it is attached. The surface of these tumors is generally quite even, and the fusiform character of the swelling is not interrupted by nodular irregularities. The rapidity of the growth varies greatly, but massive tumefaction usually occurs, and this is one of the distinguishing features between sarcoma and carcinoma. The whole disease may run its course in four months or even in two, but in the more slow growing tumors it may last for years. Hemorrhages are of frequent occurrence, either in the interstices of the tumor or upon its surface after ulceration.

The degree of pain varies greatly in sarcoma; in rapidly growing tumors it may be considerable, and in the very rapid ones it may be so severe that the disease can be mistaken for osteomyelitis; in slower growths it often does not amount to more than a dull ache, even after the neoplasm has attained some size.

It is unusual for the neighboring lymphatic glands to become involved in sarcoma; metastases occur in distant organs by the path of the blood-vessels,

as described in the section on Pathology; the lungs are usually first and most extensively involved by the metastases. Sarcoma originating in the subcutaneous connective tissue is commonly of a benign type. At first it generally forms a well-encapsulated tumor, with a very definite contour, only slightly nodular; as is characteristic of sarcoma in general, considerable size may be attained before the skin is infiltrated and becomes attached to the growth. In other words, the tumor originates beneath the skin, and this forms an important diagnostic criterion between sarcoma and carcinoma. The actual size which the neoplasm attains before the skin is involved depends upon how far beneath the skin it originates, and many of the deeper tumors may reach the size of an orange or a child's head before ulceration occurs. On the other hand, some may become attached to the skin when only the size of a pea or small nut, but even in such instances ulceration is delayed for a longer time than would be the case in epithelioma.

Another distinguishing feature between sarcoma and carcinoma is the age at which the disease develops. It is undoubtedly true, within certain limits, that both sarcoma and carcinoma become more frequent as age advances, but it is also true that sarcoma appears at a much earlier period than carcinoma. Isolated instances of carcinoma may occur in young children, and we ourselves have seen epithelioma of the face as early as at 18 years of age. But it is not at all unusual for sarcoma to be found in babies, and it is of frequent occurrence in the second decade of life.

The appearances of carcinoma are, perhaps, even more characteristic than

those of sarcoma. This is largely due to its early ulceration, and to the very typical character of the latter. We may limit our description to epithelioma of the skin and use this as a type of the disease.

In the very earliest stages of epithelioma there may be nothing more than a rose-colored dot of congestion, or a little excrescence, or roughening or scaling at one circumscribed spot. Hyperkeratosis seems to be a constant feature of the early stages of the squamous-cell variety, so that in these cases the earliest symptom is a persistent scale, which later appears as a scab, now and then dropping off and generally leaving a bleeding surface. The basilar-cell epithelioma, on the other hand, usually begins as a minute, solid nodule, and this gradually enlarges so that there is a definite stage of solid tumefaction before ulceration occurs. The basilar-cell epithelioma may then form circumscribed ulcerations of a characteristic appearance, or it may spread first beneath the epidermis over a large area without ulceration. After ulceration has occurred the same description may apply to both the basilar and squamous type of tumor.

The ulcer of epithelioma presents a crater-like appearance; the edges are raised and definitely indurated; the whole growth has a minutely nodular surface, and this characteristic is particularly well developed in the raised peripheral border. Preserving these characters the ulcer increases in size by spreading at the periphery; the tendency for epithelioma of the skin to invade the deeper structures is very slight.

Epithelioma of this basilar-cell type is of very slow growth. Its progress may be insignificant during a period of

even ten or twenty years; usually, however, during five years' time it becomes threatening. The squamous-cell variety, on the other hand, is much more rapid in its growth, and in one year's time it can become very dangerous. This type also invades the tissues more deeply, and it is this form of tumor which attacks the mucous membranes. Epithelioma of the tongue and walls of the oral cavity are of this type. Its greater degree of malignancy is also manifested by the frequency with which it forms metastases; these metastasizing forms are so rare in epithelioma of the basilar-cell type that they are curiosities, but in at least two of my own cases metastases have been present. In the squamous-cell epithelioma metastases are of regular occurrence; the regional lymph-nodes are first involved, and, if life is prolonged, metastases occur in other portions of the body before death takes place from the local disease.

From epithelioma of the tongue and the walls of the oral cavity metastases rarely get beyond the regional lymph-nodes, and this constitutes one of the safeguards against this most deadly form of tumor. In the majority of autopsies, which the writer has performed, death has generally been due to exhaustion from local recurrence and recurrence in the regional lymph-nodes; metastases have not been present in other portions of the body.

The symptoms, then, of the later stages of squamous-cell epithelioma of the skin or mucous membrane consist in the rapidly growing, characteristic ulceration, the enlarged regional lymph-nodes, a gradual emaciation and development of cachexia, and foul discharges, with repeated hemorrhages from the tumor which exhaust the pa-

tient's strength. The absorption of toxic products, the result of saprophytic bacteria and the products of proteolytic enzymes, induces a systemic intoxication; this toxemia may be accompanied by a low grade of fever, and is always partially responsible for the progressive loss of flesh and strength. As the growth increases in size and presses upon the neighboring terminal nerve twigs, it causes constant pain, which still further exhausts the patient; through these various means death ensues.

Perhaps the most characteristic train of symptoms occurs in cancer of the breast. We first have the occurrence of a lump; this is movable with the breast, upon the deeper layers of muscles, and the skin can be freely moved over it; there may at the same time be some pain or discomfort. Slowly the lump increases in size, and the skin begins to be wrinkled and drawn in. The nipple is retracted, and the tumor moves less freely upon the deeper tissues. Palpation at various times from the onset will reveal nodular enlargements of the axillary lymphatic glands, and later on of the supraclavicular glands. Finally, the skin necroses from pressure, and the tumor-tissue is exposed by ulceration; in the mean time the neoplasm has been steadily increasing in size, and hemorrhages occur from slight traumas. The patient finally succumbs by exhaustion due to these processes, or from interference with the function of important internal organs, as the lungs, liver, etc.

These processes vary greatly according to the type of tumors; in six weeks' time, and even less, we have observed the development of an inoperable tumor with all the characteristic symptoms. On the other hand, where the

neoplasm is composed of much fibrous connective tissue, years, even ten or twenty, may elapse before serious conditions are reached.

The symptoms as well as the pathology of melanoma of the skin deserve separate consideration; these tumors form a very definite class by themselves, and certain peculiarities which they present, both pathologically and clinically, render them of special importance. The nature of their early stages has been the subject of much discussion, but, as already stated, they are commonly believed to originate in the so-called non-vascular nevi and pigmented moles. The ordinary harmlessness of these small affairs is well recognized, for the vast majority of them remain as such throughout life. Every now and then, however, one will begin to increase in size, and such a patient will ultimately die of generalized melanoma. When one of these tumors begins to increase in size, it commonly does so very rapidly, and from the start the tumor is most malignant. Metastases occur very early and are very apt to form in the skin, so that the surface of the body may be covered with multiple, pigmented nodules. The neighboring lymphatic glands are also very frequently involved, so that these tumors present quite an exception to the usual history of other forms of sarcoma. When the primary tumor occurs in the eye, the growth breaks through the sclera into the orbit; it also follows the optic nerve backward, and secondary processes develop within the cranium. In their very malignant tendencies, coming on suddenly after long periods of quiescence, these tumors form a class entirely alone.

The clinical course of lymphosarcoma is more appropriately treated

under diseases of the lymphatic system, and that of the malignant adenomata under diseases of the various organs.

Duration of Cancer.—There is considerable difficulty in estimating the actual duration of cancer. Few patients recognize the actual beginning of the disease. A study of the disease from this standpoint reveals that death rarely occurs as a result of the disease itself, but in almost every instance is due to some mechanical cause, as a stenosis, compression, perforation, or hemorrhage. Very frequently also the first symptoms of the disease are of a mechanical nature, the disease remaining absolutely latent until the function of some important organ is interfered with. The beginning of the disease and the occurrence of the first symptoms seldom coincide. The disease is shortest in cancer of the orifices of the digestive tract and longer in cancer of larger cavities. Often a short course will mean a latent period.

[The following table, copied from Carl Otto (Second International Congress on Cancer, 1910, 429), from whom the above conclusions are also taken, illustrates these points for cancer of the digestive tract:—

	Esophagus.	Cardia.	Stomach.	Pylorus.	Intestine.	Pancreas.	Biliary system.
1 to 14 days	1	1	5		
1 month.....	7	..	5	1			
2 months.....	10	2	16	6	4	7	3
2 to 4 months....	14	4	12	8	6	16	3
4 to 6 "	11	5	8	7	7	5	2
6 to 8 "	6	2	2	4	3	9	1
8 to 10 "	1	1	2	2	4		
10 to 12 "	1	1	1	6	2	1	
1 to 4 years.....	5	2	4	6	4		3
At autopsy	1	..	8	4	..	1	
No clear cases	2	..	2	5	2	..	3
Totals	58	17	61	50	37	39	15

Thiem gives the following table, showing the duration of cancers of various organs:—

Duration of cancer.	First subjective symptom to diagnosis.	From time of diagnosis to death.	Total development time.
	Months	Months	Months
Gall-bladder cancer.....	4.2	4.0	4.6
Liver cancer.....	4.7	2.7	7.4
Esophagus.....	6.0	4.0	9.3
Uterine.....	6.2	4.4	10.6
Stomach.....	7.0	1.8	8.8
Throat.....	7.5	1.5	10.0
Intestine.....	8.6	4.5	13.1
Breast.....	9.1	19.2
Various skin.....	8.0		
Larynx.....	8.9		
Legs.....	25.0		
Face and head.....	45.6		

H. H. JANEWAY.]

DIAGNOSIS.—Aside from the aid in diagnosis of cancer to be obtained from the clinical features of cancer, the characteristic appearances or objective symptoms of the disease in its various locations and forms, and the general subjective symptoms, many attempts have been made within recent years to perfect some clinical test pathognomonic of cancer, which would enable us to diagnose the disease early.

The writer found—and his view has been confirmed by Blumenthal and others—that in suspected malignant growths, a rise of temperature following a rectal injection of potassium iodide (4 Gm.—1 dram—with sodium bicarbonate 2 Gm.—½ dram—and water 90 c.c.—3 ounces) differentiates malignant growths from syphilis. He compares this reaction to tuberculin and deems it equally specific. M. P. Michailoff (Roussky Vrach, Apr. 6, 1913).

The diagnostic value of potassium iodide reaction in cancer is comparable to that of the tuberculin reaction in tuberculosis. R. Robinson (Bull. de l'Acad. de Méd., Paris, Dec. 16, p. 544, 1913).

Too little importance has been attached to continued high fever in malignant tumors. That it occurs in a considerable number of cases has been noted and reported by various authors. The writer reports a personal example of continued high temperature in adenocarcinoma of the kidney. Of 475 cases reported by Freudweiler, 189, or 39.8 per cent., had fever. J. Phillips (*Amer. Jour. Med. Sci.*, Feb., 1915).

Both the urine and blood have been extensively investigated for changes characteristic of cancer.

Fuld (*Berl. klin. Woch.*, 1910, xlvii, 1062) has found that in carcinoma pepsin is absent in the urine, while in other pathological conditions which might be confused with cancer, even in achylia gastrica, pepsin is present in the urine.

Acid Oxyproteid Test.—Solomon and Saxl (*Wien. klin. Woch.*, 1911, xxiv, 449) have demonstrated an increase of oxyproteid acid in the urine of patients in whom carcinoma is growing. They state that their first publication is confirmed by K. Kondo in a work which reports findings in 500 cases and is yet in the press. A number of other conditions, however, particularly severe liver diseases, abscess and cirrhosis, enlargements of spleen, and pregnancies, will also give an increase in this same substance. Acid oxyproteid is a polypeptide, and Sorensen has introduced a simple method for its estimation by titrating with formol.

In their own paper 81 cases of cancer were tested, and, of these, 61 gave a definite positive test, 10 a weak reaction, and 10 were negative. They consider that their test is serviceable for the diagnosis of small growths.

Salkowski (*Berl. klin. Woch.*, 1910, xlvii, 533) has introduced a closely re-

lated test. The acid oxyproteid fraction in the urine is a mixture of polypeptide bodies arising from incompletely oxidized albuminous derivatives, and forms part of the nitrogenous components of the urine which are insoluble in alcohol. The same author (*Berl. klin. Woch.*, 1910, xlvii, 1796) designates the nitrogenous bodies precipitated from the urine by alcohol as colloidal nitrogen, and in a number of papers he has shown that the proportion to the total nitrogen in the urine is increased in cancer even in its early stages. The normal relationship of the colloidal nitrogen to the total nitrogen is 3 to 3.5 per cent. In carcinomatous urine the percentage is increased to 7.5 per cent. to 9 per cent. By heating the urine this colloidal nitrogen is split into amino-acids and can be titrated with formol after the method of Sorensen (*Biochem. Zeitschr.*, vii, 45). Gross (*Med. Klin.*, 1911, vii, 778) failed to confirm Salkowski's work.

The blood has been investigated by a variety of pathological procedures in attempts to find an early specific test for cancer. It has been tested extensively for the presence of isohemolysins. Crile, of Cleveland (*Jour. Amer. Med. Assoc.*, 1908, li, 158), attempted to show that in over 90 per cent. of cases the blood-serum of cancer patients had the power of destroying the red blood-cells of a normal individual when they were washed and suspended in physiological salt solution. No one else was able to confirm Crile's results.

A study of the leucocytes with relation to their form, ameboid movement, death form, etc., in cases of malignant diseases, led the writer to the following conclusions: If the smear shows neutrophilia, and fat drops in many of the neutrophils; if

the nuclei of the neutrophils are largely multifid, the case is one of a coccal infection of great or very great severity. If the smear shows a relative abundance of lymphocytes (especially of the very small variety); if there is no leucocytosis; if multifid nuclei preponderate, the case is almost certainly not one of malignant disease. If there is neutrophilia, with bizarre forms, or pseudopods in number; if the lymphocytes are in many instances showing ameboid outlines; if the monocytes show ameboid nuclei the case is almost certainly one of malignant disease. Gruner (Brit. Jour. Surg., Jan., 1916).

Antitryptic Index.—A considerable number of papers have appeared upon the antitryptic index in cancer. Blood-serum possesses the power of inhibiting the digestive action of trypsin. Various methods have been devised, but in general the principle of the reaction consists in estimating, upon plates or tubes of casein or beef-serum, the digestive action of a 1 per cent. solution of trypsin mixed with the blood-serum to be tested, diluted to varying degrees, and comparing its digestive action with similar strengths of trypsin unmixed with serum.

Brieger and Trebing (Berl. klin. Woch., 1908, xlv, 1041) showed that the normal inhibitory power to tryptic digestion was increased in 90 per cent. of their cases of cancer, but also they noticed that the same increase occurred in other conditions, particularly in suppurative conditions.

Von Bergmann and Meyer (Berl. klin. Woch., 1908, xlv, 1673) confirmed these results, and also Herzfeld, Roche, Hart, Beeker, and Landois; but positive finding also occurred in 24.2 to 42.5 per cent. of other affections.

Katzenbogen (Berl. klin. Woch., 1911, xlviii, 1840) comes to the following conclusions: 1. All patients

in whom there is a considerable destruction of leucocytes, pancreatic disease, suppurative conditions, pregnancy (placental ferments), or cancer show a high antitryptic index. 2. If clinically it is impossible to distinguish between a benign and malignant new growth, a high antitryptic index is to be regarded as a decisive factor. 3. In suppurative conditions a high index indicates a favorable prognosis, and *vice versa*.

The writer examined (by the Roger and Sovignac methods) the action of antitrypsin on 32 patients whose cases were either diagnosed clinically as cancer cases, or proved to be so at the necropsy. Sixty-three per cent. proved positive. The activity of antitrypsin was greatly influenced by the position of the cancer, and by the degree of cachexia. When the cancer developed in an alimentary organ such as the stomach, or the liver, the increased activity of antitrypsin in the serum was remarkable; while in the case of cancer of the uterus or penis, the increased activity was comparatively small. In the case of non-cancerous diseases, the activity of antitrypsin in the serum was either normal, or only a little increased, except in cases of pregnancy, puerperal women, chronic suppuration, and pulmonary tuberculosis, in which increased activity of antitrypsin in the serum is a recognized fact. Kurata (Bull. of Naval Med. Assoc., Tokyo, Aug., 1917).

Complement Deviatory Power.—Caan (Münch. med. Woch., 1911, lviii, 731) has tested the blood for its complement deviation power in cancer after the technique of the Wassermann reaction in syphilis. Of 85 cases 35, or 41 per cent., gave a positive result, though a weak one. Barratt (Brit. Med. Jour., 1910, ii, 1440) obtained such a deviation of complement in one-third of the cases of mice

which were hosts of tumors, but could not obtain it. at all among human beings.

The activation by cobra venom of the hemolytic action of the serum in the deviation of complement test occurs only with serum from persons with malignant disease. With rabbit red corpuscles, a positive reaction was pronounced in the writer's total of 53 out of 64 persons with carcinoma. In all the other 11 cases, the reaction occurred, but not until after the 20th hour, and these are considered negative. In 62 persons with benign tumors there was no trace of a positive reaction. He now uses 0.1 c.c. (9 minims) of a 1 to 20,000 solution of cobra venom, *e.g.*, 1 part of a 1 to 5000 solution of venom in 3 parts of normal saline. The author urges the value of the cobra venom reaction as an aid in the diagnosis of malignant disease. C. B. Farmachidis (*Riforma Medica*, May 18, 1918).

In addition, von Dungern (*Münch. med. Woch.*, 1912, lix, 65), reviewing the negative work of Engel, Ravenna, de Marchio, Philosophow, Barrat, Grafe, Weil, Hirschfeld, and the somewhat more favorable work of Simon, Charles and Thomas, Sisto and Jona, Sampietro and Tesa, states that he himself, by a more careful technique, has been able to make of this test an almost absolutely dependable one. He uses extract of the tumor tissue obtained with 98 per cent. ethyl alcohol, allowing six times as much alcohol as tumor tissue and extracting from twelve to eight hours. This is diluted with an equal quantity of normal salt solution to which is added $\frac{1}{20}$ cm. of serum to be tested, and as complement guinea-pig serum $\frac{1}{20}$ cm. He uses cows' blood-cells capable of being dissolved by the serum sensitized to such a degree that

the solution of the cells follows in three-fourths hour at 37°. He has obtained a positive test in all cases of malignant tumors, 42 in number, and negative findings in all other conditions, 13 in number, except syphilis. Some benign tumors, especially one case of myoma, gave a positive result.

Cytolytic Power.—Monakow (*Münch. med. Woch.*, 1911, lviii, 2207) has reviewed the literature and quotes Freund (*Kamäner, Biochem. Zeitschr.*, 1910, xxvi, 312; *Wien. klin. Woch.*, 1910, xxiii, 1221), who reported that serum from cancer patients will fail to dissolve the patient's cancer cells when in contact with them at 37° for twenty-nine hours, while normal serum possesses such a power. C. Neuberg (*Biochem. Zeitschr.*, 1910, xxvi, 344) confirmed these results. So also Stammeler (*Münch. med. Woch.*, 1911, lviii, 1043), Kraus, Graff, and Ranzi (*Wien. klin. Woch.*, 1911, xxiv, 1003), Simon and Thomas (*Jour. Amer. Med. Assoc.*, 1908, li, 915) have reached contradictory results.

A serum is considered as possessing normal cytolytic powers against cancer cells when the number of such cells suspended in salt solution and mixed in proper proportions with the serum is reduced after contact to 50 per cent. in comparison with the controls.

Monakow's results gave a positive reaction in 86 per cent. of the cancer cases. Of 52 sera from non-cancerous individuals 13 acted as the 86 per cent. of cancerous sera had, *i.e.*, failed to dissolve 50 per cent. of the cells, and 5, or 9.6 per cent., were doubtful. Only 65.8 per cent. of the control dissolved 50 per cent. or more of the cells. He concludes, therefore, that with care the reaction is a valuable diagnostic aid.

Meiostagmine Reaction.—The writer has left for the last the consideration of the meiostagmine reaction because at present it appears to be the most important of all of the general reactions of cancer.

This reaction measures the change in the viscosity of dilutions of serum from cancer patients resulting from the mixing and incubating the same for two hours with a properly diluted antigen obtained by extracting the dried tumor tissue with methyl alcohol. Five Gm. of dried tumor tissue are extracted with 25 c.c. of methyl alcohol.

This is diluted 100 times and 1 c.c. of such a dilution is mixed for the purpose of the test with 9 c.c. of a 1:20 dilution of the serum in 85 per cent. sodium chloride solution. The addition of acetic acid in quantities to make a proportion of 1:1000 of acetic acid in the total mixture increases the intensity of the reaction.

The difference of superficial tension between the test mixture and its control is measured by viscometer, Traube's stalagmometer being a convenient one.

Ascoli and Izar have developed the test and published their experiences with it during the years 1908-1910 (Münch. med. Woch., 1910, lvii, 62, 403, 954, 1170, 2129). They have obtained out of 100 cases of malignant new growths 93 reactions which gave a sufficient change in superficial tension to be designated as positive, and failed to obtain such a change in all of 103 cases of various other non-cancerous diseases. Various authors have in the main confirmed Ascoli and Izar's results.

A more dependable antigen than lecithin for the meiostagmine reaction can be prepared from the spindle cell

sarcoma of white rats. Positive results were obtained with it in 110 specimens of serum from clinical cases of cancer or from rats with cancer. The findings were positive in all except 3.64 per cent. of the human cases. Roffo (Revista del Inst. Bacteriol., Buenos Aires, Nov., 1917).

The writer gave the meiostagmine reaction a trial and found it disappointing. All the cancer patients gave a positive response, but so did all but 5 of 17 other patients free from malignant disease. Salvesen (Norsk Mag. f. Laegevidenskaben, Mar., 1918).

Reaction in Vivo.—Subsequently Izar (Berl. klin. Woch., 1911, xlviii, 1748) improved his technique and so modified the test that the reaction is conducted *in vivo*. The reaction *in vivo* depends upon the fact that an aqueous emulsion of either a methyl alcohol or ethereal extract of tumor tissue which is treated for either one hour at 50° or two hours at 37° is found to develop peculiar active toxic properties. When an antigen extracted in the manner described is mixed with blood-serum and heated for one hour at 50° and then centrifuged, it is found that a toxic principle is developed in either the precipitate or filtrate, according as the serum is taken from respectively an individual suffering from cancer or from a normal person.

The toxicity of the precipitate or filtrate is tested by injecting it into either rabbits or guinea-pigs. Such animals, after injection, develop dyspnea, convulsions, vomiting, rectal evacuations, paralysis of the extremities, and death, if the test is positive within twenty-four hours. He has tested 21 definite tumor cases, 19 of which gave a positive reaction. Of 32 non-cancerous patients 2 gave a positive reaction.

Contrasting this reaction with the meiostagmine reaction conducted *in vitro*, he obtained, out of the same 53 cases, identical reactions in 48 cases, with the exception of 5, so that in the same series of cases the meiostagmine reaction *in vitro* gave 5 more anomalous results than the reaction conducted *in vivo*.

Special diagnostic chemical tests have been devised for the early recognition of cancer of the stomach. These are more properly dealt with in that portion of this work which treats specially of the diseases of the stomach: but because such a large proportion of cancers occur in the stomach the following tables have been arranged, together with the references of some of the more important tests. These tests are:—

1. For the estimation of the diminution or absence of hydrochloric acid in the stomach contents of patients with cancer of that organ.

2. For the power of the digestion of normal gastric juice upon raw catgut (Sahli desmoid reaction).

3. For the increased percentage of albumin in stomach contents of patients with gastric cancer (Solomon's test).

4. For the hemolytic power of the stomach contents in gastric cancer.

5. For the presence of a polypeptide-splitting ferment in the gastric contents of patients with cancer of the stomach (glycyl-tryptophan test). (*See table on following page.*)

Abderhalden Test.—This test based on the belief that the presence of certain morbid conditions including cancer in any structure brings about the formation of protective ferments is reviewed under **HEMATOLOGY** in the fifth volume.

TREATMENT.—The subject of the treatment of cancer covers a wide field, and it is wide because we yet know so little in regard to the real nature or cause of the neoplasms which are grouped under this name. Pathology has not helped us much as to the reason for their appearance and malignant course, nor has it afforded us much guidance as to treatment, except to emphasize the necessity of very radical extirpation, including the glands and neighboring tissue when the knife is resorted to.

If we accept the modified Cohnheim view, as already presented, that neoplasms originate from embryonal misplacement of tissue, which takes on virulent action later, and still more so if we believe that some cancers originate by direct transformation of the normal body cells, the question still remains unsolved why this malignancy occurs in one individual and not in another; also why a melanotic deposit which has long remained innocent may subsequently become malignant.

When we turn to the results of experimental work on animals, as already detailed, we find that, while some malignant tumors can be transmitted from one animal to another, under certain circumstances, still, in some mysterious manner, a degree of immunity can be also created under certain conditions of inoculation; exactly what this change is has not been demonstrated, and perhaps will defy ultimate analysis.

So that, while modern science rejects wholly the idea that any of the forms of cancer are "diseases of the blood," in the older acceptation of the expression, and while all experience shows that there is no internal remedy, or remedies, which will surely check the

DIMINUTION OR ABSENCE OF HYDROCHLORIC ACID.

References.	Cancer cases.		Suspected cancer cases.		Other affections.	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Von Velden, Deut. Arch. f. klin. Med., 1879, xxiii, 31	8					10
Wilcox, Quart. Med. Journ., 1909, iii, 93 ..	17					
Graham, Quart. Med. Journ., 1911, iv, 315..	nearly all					
Paulon and Tidy, Quart. Med. Journ., 1911, iv, 449	39	4				
Moore, Proc. Roy. Soc. of London, 1905, lxxvi, B. 138	11 (cancer, a		ny location) a		nd in all but 1	
	of 6 ot		hers on ly min		ute trac e.	
SAHLI DESMOID REACTION.						
Eichler, Berl. klin. Woch., 1905, xlii, 1493 ..	7				4	19
Kuhn, Münch. med. Woch., 1905, lii, 2412..	7				12	35
Kaliski, Deut. med. Woch., 1906, lii, 185 ..	6		2			16
Boggs, Johns Hop. Bull., 1906, xlv, 313 ..	7		1	1	13	11
SOLOMON TEST.						
Solomon, Deut. med. Woch., 1903, xxix, 547						
Fraenkel, Med. Klin., 1910, vi, 1098	13	8	1	7	1	17
Grafe and Rohmer, Deut. Arch. f. klin. Med., 1910, c, 597	38	4	8	6	5	72
Liviersto, Berl. klin. Woch., 1910, xlvii, 1452	19, 17, 14	4, 6, 9			21, 34 18	12, 19 25
Fraenkel, Münch. med. Klin., 1910, vi, 1098	15	6	4	4		
Fabien, Deut. med. Woch., 1910, xxxvi, 554	8	5	1	0	8	10
Kunz, Inaug. Diss., 1908	27	1			3	10
Sisto and Jona, La Clin. Med. Ital., 1909, xlviii, 282	7	4	2			
GLYCYL-TRYPTOPHAN TEST.						
Neubauer and Fischer, Deut. Archiv f. klin. Med., 1909, xcvi, 449	17	2	6	4		26
Lyle and Kober, N. Y. Med. Journ., 1910, xci, 1151	6					5
Elsenberg, Berl. klin. Woch., 1911, xlviii, 705	2	5			5	7
Oppenheimer, Deut. Zeit. f. klin. Chir., 1910, ci, 293	9		1	6		24
Kuttner and Pulvermacher, Berl. klin. Woch., 1910, xlvii, 2057	18	21	4	9	35	76
Ley, Berl. klin. Woch., 1911, xlviii, 119 ..	2	2	2	6	4	4
Pechstein, Berl. klin. Woch., 1911, xlviii, 375	14	5	1	2	1	9
Hall and Williamson, Lancet, 1911, i, 731..	6	3	2	0	0	20
WEINSTEIN'S TRYPTOPHAN TEST.						
Weinstein, Jour. Amer. Med. Assoc., 1910, iv, 1085	19	0		2		20
Sanford, Arch. Int. Med., 1912, ix, 445 (rendered the death blow to glycyl-tryptophan test).	4	18		10	4	20

progress of the disease, certainly in advanced cases, all study, whether clinical, pathological, or experimental,

points to the fact that there is some underlying, hidden cause which leads to that aberration in the action of

tissue-cells which we call cancer. It is possible to conceive of such an underlying hidden cause as residing in only the cells themselves, or in some abnormal chemical constitution of the plasma bathing the cells, or in both of these possibilities acting together. Careful research upon the metabolism of cancer alone will help us to unravel these obscure problems.

The writer looks upon cancer as a general disease of which the local lesion, ordinarily excised surgically, is the result of a previous, perhaps long-standing, blood or nutritional disorder. Excision cannot be expected to eradicate the malady permanently. Laboratory and clinical evidence demonstrate that the secretions and excretions of the body, both in early and late cancer, exhibit departures from normal indicating metabolic disturbances which may influence the nutrition of the cells. Repeated laboratory experiences have demonstrated the absolute controlling effect of diet on inoculated cancer in mice and rats.

An absolutely **vegetarian diet** is the first requisite in the treatment and prophylaxis of cancer in man. It should be maintained indefinitely, excluding animal protein, even eggs and milk, though not butter, of which $\frac{1}{4}$ pound is to be taken daily by a person weighing 150 pounds. Cereals are to be freely eaten, slowly, with a fork, and with butter, not with milk and sugar, though the latter may be used moderately where it seems necessary. Perfect mastication, with thorough insalivation, is essential. As beverages, only weak tea is allowed, with some postum or other coffee substitute. Sufficient water, not iced, should be taken, commonly $\frac{1}{2}$ pint with each meal, and, hot, 1 hour before both breakfast and the evening meal. A simple, healthy life, with regular hours of eating and sleeping, a reasonable amount of exercise, are important, and should be insisted upon.

Medical treatment lies mainly along the lines of elimination, which is always faulty, both by bowel and kidneys, viz., **cascara**, in combination with other remedies, and also, often, once a week, on alternate days, 2 laxatives of **blue mass**, **colocynth**, and **ipecac**. For the kidneys **potassium acetate** is used; thus:—

R *Potassii acetatis* 3j (30 Gm.).
Tinct. nucis vom. 3iv (16 Gm.).
Fl. ext. cascara sagrada 3j-3iv (4 to 16 c.c.).
Fl. ext. rumicis (N. F.)... 3iv (120 c.c.).

M.—Teaspoonful in water $\frac{1}{2}$ hour before eating.

Iron and arsenic, phosphates and strychnine, and even cod-liver oil are also useful. Thyroid gland sometimes assists materially in removing the growth, but must be given with caution.

These patients should be seen at least weekly, and even for months or years, with careful and accurate records, urinary and blood analyses, etc. From 40 years' experience the author is convinced of the efficacy of the above non-surgical treatment of cancer. L. D. Bulkley (Address before Soc. Alumni of Bellevue Hosp., Feb. 7, 1917).

The treatment of cancer is naturally divided into: I, surgical, and, II, non-surgical. By the former is intended the complete surgical removal of all accessible disease, both in the primary site and in metastases. The latter is understood to include all other measures which have been reported on more or less favorably, either for influencing advantageously the supposed constitutional condition underlying the activity of neoplasms or for directly attacking the latter.

I. Surgical Treatment.—In the light of modern surgical development, and of the results reported by able and conscientious observers and operators,

there can be no question but that surgery has accomplished very much in the treatment of cancer. And it is believed that if competent surgery could have the opportunity of reaching the disease in its incipency the percentage of permanent successes would be even much greater. The possible achievements of surgery are illustrated by such statistics as those of Halsted in cancer of the breast, showing 42.3 per cent. of cures lasting over three years; by those of Kuster's clinic, reported by Haines, of cancer of the uterus, with 47.5 per cent. of cures lasting over five years, and those of the Mayo brothers, of 22.2 per cent. of cases of gastric carcinoma, alive and well for more than three years after operation. Confirmatory results have been reported for cancer of breast by many surgeons.

The percentages above mentioned are simply illustrative of what can be accomplished, and are instructive when we consider the common course of such cases when left without surgical aid. They also teach a lesson in regard to public enlightenment concerning what can be done for malignant disease, and in regard to professional education relating to the early diagnosis of such troubles. They likewise speak strongly in reproof of those, both in and out of the profession, who blindly condemn surgical operations, or who too often delay resorting to them until the disease is so far advanced that it is too late to expect favorable results.

A single word must, however, be added as to surgical procedures. In claiming for surgery such a measure of success it is understood that the necessary operations are performed after the most approved methods, and with a thoroughness far different from that belonging to older days; these

are matters which cannot be entered into here, but which are of the utmost importance.

The end-results of 1000 operations for carcinoma of the abdominal viscera from the statistics of Bunts, Lower, and the writer's own work, showed that every possible **psychic aid** should be employed to **diminish all emotional stress** incident to the operation. **Nitrous oxide** is used as an anesthetic rather than ether, as it causes less marked changes in the brain, adrenals, and the liver, and at the same time protects them to a certain extent from surgical trauma. **Anoci-association** is employed throughout the operation, because operations done under this method show no increased acidosis. Crile (*Interst. Med. Jour.*, xxii, 722, 1915).

Surgical removal undoubtedly has its limitations, which are to be determined by competent judgment in each individual case; but these are gradually lessening with advancing knowledge and skill, and the percentage of permanent success is steadily improving in the hands of many competent operators. In superficial cancer or epithelioma, when well performed in the early stages, surgical removal gives a very large percentage of cures; indeed, when very radical and in a very early stage it may almost be said that the disease rarely recurs. In later stages there is, of course, a less measure of success, and, when far advanced, cancer of any form lies beyond the reach of surgery. In but few conditions is the success of prompt, careful, and radical surgical procedure more evident than in certain cases of epithelial cancer about the face. Even cancer of the tongue often yields brilliant results when thus rightly treated.

On the other hand, in many cases of epithelioma of the face surgical re-

removal results in much deformity, which can often be avoided by the use of other measures, to be mentioned later, although care in applying them should always be exercised lest the disease progress even beyond the aid of surgery. Pronounced cancer of the lip should never be trifled with, for perfect surgical removal still offers about the only prospect of complete relief.

Much the same can be said in regard to many cases of sarcoma, although the limitations of surgery are more evident here, and, as will be seen later, other measures are of definite value in a certain class of cases. Mention has already been made of the importance of very early surgical treatment in melanotic sarcoma, although, unfortunately, this is frequently resorted to when it is already too late to obtain a successful result, and after fatal metastases have already taken place.

McCosh, in reporting a series of 125 cases of sarcoma, furnishes an account of 11 cases of his own thus treated, 5 of which had remained well for over four years.

Of 65 cases reported by Kocher, 9 remained well after three years. Reinhardt reports, out of 54 cases treated, 7 well after three years. Of 96 cases treated at von Bergman's clinic, reported by Nasse, only 4 remained well after three years; 3 of these were myeloid sarcoma, and 1 a periosteal sarcoma.

The other forms of cancer, the varieties of sarcoma and adenoma, endothelioma, etc., should always be considered first from a surgical standpoint, and other measures adopted only after having excluded the advisability of surgical removal for very good reasons. In all operations on malignant tumors ultimate success depends on

the widest possible extirpation of all diseased tissue, and even of apparently healthy tissue, for a distance around the neoplasm, together with all lymphatics, as directed in works on modern surgery; the mere excision of diseased tissue is often worse than useless.

II. Non-surgical Treatment.—This includes all other measures which have been recommended on good authority, either for combating the supposed constitutional conditions underlying the activity of neoplasms or for directly attacking or influencing the latter. They may be considered under the following heads: 1, diet and hygiene; 2, drugs and chemical agents; 3, caustics; 4, certain physical agents; 5, serotherapy.

1. Diet and Hygiene.—These cannot cure cancer, but are features never to be overlooked in the management of the disease. As an example, alcohol, certainly in excess, is most prejudicial in all forms of cancer, as is also stimulating diet of any kind; the harm from the use of tobacco in cancer of the lip and buccal cavity is well known. In most cases at all severe, a carefully regulated and perfectly digestible diet contributes much to the comfort and well being of the patient, and should be controlled by the constant care of the physician.

Of late years a number of careful observers have reported the very greatest benefit from an absolutely vegetarian diet, and in some instances have even claimed cures in advanced cases. The relative freedom from cancer of natives in the Far East, many of whom are strict vegetarians and never touch animal food, would seem to corroborate the value of a vegetarian diet.

Hygiene may also play a more or

less beneficial part, especially in severe cases, certainly in mitigating some of the distressing features of the disease. Advanced cases are too often left relatively uncared for, whereas due attention in regard to sunlight and fresh air, and proper cleanliness with antiseptics, may do much to minimize the offensiveness and distress caused by the activity of micro-organisms on the diseased tissue.

Report of successful experiments in the dietetic treatment of malignant disease in which substances in the diet promoting growth were all carefully excluded, and others added which tend to inhibit growth. On ordinary food 100 per cent. of the tumor grafts took, some growing to be larger than the body of the mouse. Given the restricted diet 10 days beforehand, none of the grafts took or grew only feebly. Tumors already established, up to 2 or 2.5 cm. in diameter, became arrested and were finally reabsorbed. Large tumors softened and decayed to a friable mass. The growth-promoting substances are certain vitamins, certain internal secretions, and certain chemical substances. The antiscorvy vitamin, and nuclein and phosphorus compounds were carefully excluded, and food denatured by heating to 125 or 130° C. The outlook for application of the principle to man is promising. E. Centanni (*Riforma Medica*, Aug. 10, 1918).

The writer collected from the literature 302 cases in which either temporary or permanent recession of a malignant tumor occurred. The causes of recession most frequently found in the series were heat and an incomplete operation. The heat may either be artificially supplied, or the result of an acute febrile infection, such as erysipelas, tuberculosis, or pneumonia. Nutritional factors, and in a few cases, fibrosis, are described as the cause of the absorption. The knowledge that spontaneous regression does occur offers some hope

that the cancer research worker may in time find some method of inducing it. G. L. Rohdenburg (*Jour. Cancer Research*, Apr., 1918).

2. Drugs and Chemical Agents.—

While no medicines can cure cancer, a carefully directed eliminant and tonic course certainly helps the patient to bear the malady, and some believe that it even wards off the trouble. Many have reported the arrest of lymphosarcoma by the proper, free employment of **arsenic** internally, and **thyroid gland** has been favorably reported on in carcinoma (see vol. i, *ANIMAL EXTRACTS*); also the use of **methylene blue**. It is needless to say that the many advertised quack remedies are worthless, and in all attempts to reach the disease by other than radical surgical operation great care should be exercised lest precious time be lost in which this latter might yield a successful result.

Hydrated magnesia and magnesium silicate—0.20 to 0.25 Gm. (3 to 4 grains) of each in a cachet twice daily—prescribed first in a case of papilloma, then in cases of epithelioma in conjunction with **arsenic pastes** locally, and finally in cases of inoperable cancer. In papillomas and superficial epitheliomas perfect results were obtained. In inoperable cancers the effects were arrest and even reduction of the tumors, marked diminution of pain, and improvement of the general condition. The author now gives the magnesia and magnesium silicate cachets in all operated cases of cancer, with the aim of preventing recurrence. They are taken only 5 days in every 10 to obviate habituation. J. Regnault (*Bull. de l'Acad. de Méd.*, July 9, 1918).

Improvement in malignant disease reported under systematic deep intramuscular injections of small doses of **quinine** well diluted, according to Castaigne's technique. The cancer loses its distressing features, and the

patient is greatly relieved and possibly buoyed up for months with an illusion of recovery. V. Delfino (Vida Nueva, Havana, Aug., 1918).

Chemical Agents.—Czerny and Caan have made extensive trials with **salvarsan**, and concluded that a therapeutic trial of it is indicated in all inoperable malignant tumors with a positive Wassermann reaction, especially in sarcomas. It has a surprising effect in lessening pain. In operable sarcoma; if a positive Wassermann reaction is present, a preceding trial of salvarsan might be made. In cachectic and weakened individuals it is contraindicated.

The use of arsenic may create a proclivity toward malignant forms of growth. Most conspicuous and frequent are epitheliomata; various forms of sarcomata and probably endotheliomata occur in the same connection, and possibly in the same individual. The writer became aware that arsenic gives proclivity to cancer and has almost abstained from its employment, advocating its use only in cases which very specially demand it. Hutchinson (Brit. Med. Jour., April 29, 1911, p. 976).

Attracting considerable attention in connection with the chemotherapy of cancer has been the frequently successful treatment of mouse tumors by the intravenous injections of **tellurium** and **selenium** in a solution of eosin as vehicle. Wassermann (Berl. klin. Woch., 1912, xlix, 4) has published surprising results on mouse tumors by using these metals. The sodium salts of these metals become reduced by cancer cells, and their oxides are deposited within the cancer cells as a black or red powder. In such a form they are readily recognized and have been employed by Gosio (Zeitschr. f. Hygiene, 1905, li, 65) as an indicator of the death of the

cancer cell. A 1 per cent. solution of these salts injected into the tumor will cause it to soften and break down. Injected intravenously the salts alone cannot cause softening of the tumors, but in combination with eosin the diffusion of the metals into the cancer cells is rapidly facilitated, and with just the right preparation Wassermann has been able to accomplish a cure of a number of mice tumors. The exact preparation of the remedy, however, has been a matter of very great difficulty.

After a daily injection of large doses of this remedy on the fourth day the tumor becomes softened and elastic. From the time of the fifth injection given at an interval of forty-eight hours after the fourth injection the absorption of the tumor sets in. After the sixth injection the site of the tumor is occupied by a hollow sac, and after the seventh or eighth injection complete healing has occurred.

Wassermann has obtained by this means a series of mice which have been cured and have remained free from recurrence. Unless the preparation has been exactly correctly prepared no effect is produced. The dose must approximate the fatal toxic dose of the remedy.

Unless all the tumor is destroyed a recurrence always results in eight to fourteen days' time, and if recurrence has set in the tumor is refractory to treatment.

These experiments have been used upon 5 strains of tumors, 4 carcinomas, and 71 sarcomas. The tumors possessed a virulency of 90 to 100 per cent. of takes. The destruction of the tumor cells is not a fat metamorphosis or a colloid or hydroscopic destruction, but rather 'a

destruction of the nucleus. It should be described as a pyknosis. Before the cell body disappears the nucleus is broken up and extruded. No leucocytic infiltration occurs on the border of the tumor, provided the same is not ulcerated before treatment. The tumor detritus is further absorbed and destroyed in the spleen, and to a slight extent such particles as escape through the spleen are destroyed in the liver; but this process is not accompanied by metastatic formation. No organs seem to suffer from the toxic effects of the remedy except the liver and spleen. The changes in the spleen may be described as a lymphatic transformation of the organ, and in the liver as a formation of small collection of lymph-cells at the division points of the portal veins. In animals without tumors a similar lymphatic transformation of the spleen occurs, but no changes in the liver. We have dealt at length on this work of Wassermann, as it is the first instance of the successful treatment of a malignant tumor, even if it is in an animal, by a chemical agent administered intravenously, and consequently of very great significance.

C. E. Walker gave **selenium** in a series of cases one of which he reports at length. The patient was a woman of 60 years who had been operated upon fifteen years before for cancer of the breast. At the time of examination she was cachectic, the output of sulphur in the urine was greatly diminished, and the liver was enlarged and evidently the seat of a secondary cancerous growth. Treatment was begun July 27, 1910, with a milligram ($\frac{1}{65}$ grain) of selenium oxide (SeO_2) three times a day. By September 2d there had been a gain in weight of $2\frac{1}{2}$ pounds and the liver dullness had receded two finger-

breadths. During the treatment the patient at times gave evidence of renal irritation, which the author attributed to the rapid breaking down and excretion of the cancer cells—possibly the same thing that killed the mice in the Wassermann experiments. The improvement in the general condition was, however, continuous, and up to the time of the report, eighteen months after the beginning of treatment, there had been no relapse. E. G. Kessler (N. Y. Med. Monats., Jan., 1912).

R. Oestreich (Zeit. f. Krebsforsch., Bd. xi, 44), noticing that cartilage and arterial walls are very rarely invaded with cancer, has suggested the treatment of malignant new growths with the injection of **sodium chondroctin sulphurate**, the most characteristic constituent of these tissues; 0.1 Gm. is injected subcutaneously. The only results accompanying this form of treatment have been a necrosis in the tumor tissue and leucocytic infiltration around it, some general reaction accompanied with an increase in the body weight, and a strong local reaction.

Organotherapy.—Another form of treatment of cancer, perhaps incorrectly classed under the heading of the chemical therapy of tumors, is the attempt to cure cancer by the injection of **thymus extract**. Frederick Gwyer (Annals of Surg., 1908, xlvii, 506) has treated 16 cases of cancer in this manner. He has obtained a temporary improvement in 10 cases and no result in 6. The *rationale* of this form of treatment depends upon the rarity of cancer in the young and the functional activity of the thymus at this time of life.

Takaki prepares a powder from fresh calf's **thymus gland** which is given by the mouth in doses of from 0.01 to 0.05 Gm. ($\frac{1}{60}$ to $\frac{1}{120}$ grain) twice

a day between meals. To avoid indigestion, it is best to give quite small doses to begin with, and with sodium sulphate. One of the chief effects is diminution of the pain, so that it is particularly in patients who suffer from this symptom severely that thymus treatment is likely to be most useful. There seems to be a decidedly increased tendency on the part of the malignant tissues to undergo suppuration and necrosis. Although the treatment will not bring about radical cure, it seems certainly worth while adopting it in advanced cases, especially when there is pain. Takaki (*Sei-i-Kwai Med. Jour.*, Sept. 30, 1910).

Several cases of malignant tumor surgically inoperable were treated with **thymus gland** alone or in any of several combinations. In almost all, nutrition was markedly improved, the patients gaining in weight from 1 to 14 pounds. The hemoglobin and red cells also increased; the patients felt stronger, and the pain was greatly diminished. The discharge and bleeding were lessened and in a majority of cases stopped. The local changes were variable. The glands diminished in size and in some cases disappeared, and the tumors themselves showed a cessation of growth and in some cases a temporary decrease in size. In 1 case (recurrence after amputation of breast) a complete disappearance occurred. The 48 cases observed cause the authors to conclude that thymus extract, when given for three to five weeks, markedly influences malignant tumors. After this comes a period of quiet with neither progress nor retrogression for about two weeks, after which the tumor either gradually increases in size or remains for a long period stationary, or, rarely, disappears altogether. Better results were obtained from thymus than from any of the other glands or various combinations of them. Rohdenburg, Bullock, and Johnston (*Archives of Intern. Med.*, April 15, 1911).

Pluriglandular therapy when it includes **thyroid** and **sexual glands** induces in a cancerous growth a retrogressive change. In some it checks the active growth of the tumor, and in a limited number causes its apparent disappearance. It probably lessens the abnormal alkalinity of the blood by stimulating the metabolism. H. N. Das (*Calcutta Med. Jour.*, Nov., 1917).

The writer considers as great progress the result of recent research by Kaminer and others showing that malignant growths can be influenced by **serum** and **organ extract** treatment; also that **diet** has an influence on the growth of cancer. **Thymus extract** in particular seems to destroy cancer cells in vitro, even when diluted 32 times, or destroys 55 per cent. and 32 per cent. diluted 23 and 24 times. This suggests the possibility of destroying cancer in the living body by injection of thymus extract, which may also aid in the elucidating the etiology. He adds that the best results to date with thymus extract have been obtained with fresh, unheated thymus extract. His own experience with it is still too recent for a final decision, but the patients bore daily injections of 10 c.c. (2½ drams) without signs of intolerance, no general or local reaction or anaphylaxis. Denmark has no general institution for cancer research, and the writer urges others to follow this promising line of study, investigating the physiology of the thymus of different ages, the behavior of the thymus in persons with cancer, the effect of thymus extract on incipient cancers, and the species of animals that yield the most effective thymus extract; dog thymus to date has shown greater cancer destroying power than rabbit thymus. The thymus extract should be standardized and the essential principle isolated if possible. It will be interesting to see how injections of thymus extract affect the inoculability of mouse and rat cancers, and whether preliminary injections of thymus extract will ward off the development of Fibiger's nematode cancers in rats, and the Japanese

cancers in rabbits, and, finally, whether they may not prove effectual in warding off recurrences in man after operations or radiotherapy. S. Nordentoft (Jour. Amer. Med. Assoc., from Ugeskrift for Laeger, Jan. 23, 1919).

Epinephrin, adrenalin, or any other reliable active principle of this portion of the adrenal gland, in 1 to 1000 solution, painted or swabbed over the surface of the growth relieves pain, arrests hemorrhage, and even tends, by causing constriction of the vessels, to cause partial retrogression of the growth. Injections of 10 minims of the same solution into the tumors enhance further the latter effect; but the injections should be administered under strict asepsis, and after carefully sterilizing the surface with a solution of hydrogen peroxide.

[The local effects of **adrenalin** in this connection were observed by C. Fiessinger, who attributed them to its effect on vessels of the neoplasm. In cancer of the rectum, he found that painting twice daily with 30 to 100 drops of a 1:1000 solution of adrenalin in a tablespoonful of water decreased the rectitis, checked the discharge, and brought about a temporary diminution of the growth. Mahn had previously obtained prompt results by simply painting the growth with the 1:1000 solution. The neoplasm partially retrogressed, then remained stationary, free from pain or hemorrhage, the patient being in apparently perfect health. In 4 other cases the results were also satisfactory. Berdier and Falabert tried injections in advanced cases and found that they caused diminution of the tumor and of the adjoining glands, abolishing pain and increasing the patient's weight. The injections were made into the tumor, or, when this was inaccessible, into the arm, or over the organ involved. J. E. Rhodes reported a case of inoperable nasopharyngeal sarcoma in which the injection of adrenalin into the growth, together with local swabbing and spraying, caused marked reduction in size and alleviated the pain, though the patient's life was not prolonged. J.

Price-Brown also found that adrenalin checked the circulation in sarcoma and lessened bleeding. Ed.]

Adrenal gland, known as **suprarenalium siccum** in the U. S. P., is of advantage in these cases to prevent anemia by supplying the blood with the oxidizing constituent of the hemoglobin. Three grains three times daily with *iron*, preferably Blaud's pill, one grain, prolong life by counteracting the progress of the cancerous cachexia.

[The usefulness of adrenal gland in this connection was illustrated by one of Dr. Sajous's cases of advanced uterine cancer in which life was considerably prolonged, improvement of the patient's condition having become manifest soon after the use of the gland had been begun. It seemed also to prevent severe pain, doubtless by causing constriction of the arterioles, thus reducing the local hyperemia and swelling. The patient died, in fact, without knowing that she had suffered from cancer. Ed.]

The active principle of the **suprarenals** injected around an experimental tumor on mice almost invariably led to its subsidence. From 5 to 13 injections accomplished this in rats. These results suggest a trial in suitable cases. Reicher (Deut. med. Woch., July 21, 1910, xxxvi, 1356).

The simultaneous use of **radium**, **thyroid gland**, and **adrenal gland**, the two latter in the above-mentioned doses, improves the likelihood of recovery beyond those offered by radium alone.

(See article on Animal Extracts in vol. i, for additional data on the treatment of cancer by organotherapy.)

Local Destructives. — In earlier years, before the better knowledge of metastasis, and before the advances of modern surgery, and before employment of the X-ray, etc., there was much use of destructive methods, in hopes of totally removing neoplasms

and replacing them by healthy scar-tissue, and the number and variety of agents recommended for this purpose have been very great. It may be said that these have gradually been employed less and less by the medical profession, although they are still a great field of enterprise for advertising quacks. While they have their value in certain rare instances, it is doubtful if, as often used, they do not do more harm than good. A striking illustration of this is found in the use of nitrate of silver, with which it was formerly so common to "touch up" rebellious sores; by this means innumerable instances of mild epithelioma have been goaded into lesions of most serious character, beyond hope of relief by any means; this is especially true of the disease within the mouth or on the face.

Caustics have also been employed in carcinoma in many deeply seated locations, often with disastrous consequences, resulting not only often in death from exhaustion, but also in the disease recurring *in situ*, and in metastases which could not be thus reached. Caustics are very rarely justified in cancer of the lip, and never in large or deeply seated tumors, as in the breast.

But, on the other hand, caustics of various kinds are occasionally of service, and if used just rightly, in proper cases, may eradicate the disease. The principle to be applied to them is that they must be radical, destroying deeply and thoroughly, even to some distance beyond the diseased tissue; if there are already metastases, however, the ultimate result must be unfavorable. Space does not permit enlarging on this subject or giving details of treatment, but an illustration of what is intended is found in the use of the

well-known **Marsden paste**, of arsenious acid, in certain cases of epithelioma. When rightly handled this certainly cures many cases permanently, leaving most satisfactory scars; the same is more or less true of **caustic potash**, **Canquoin's paste**, **Bougard's paste**, and perhaps others.

Albert Carson states that twenty-five years' experience in the treatment of malignant new growths with many escharotics has taught him that those agents which are the most actively hygroscopic produce the most perfect granulating surfaces. He therefore uses in combination those most active of all escharotics, **potassium hydrate** and **zinc chloride** (granular). These are equally applicable both to skin and to mucous surfaces. In the mouth and throat he uses a combination of chromic and carbolic acids.

The technique of his work in all cases is to outline the growth by palpation, seeking its most distant ramifications. This done, he makes an application of the potassium hydrate, completely covering the entire growth, and extending the application in all directions as far beyond its most remote infiltrations as the situation of the growth will admit of doing, never with a view to conservatism. The application should be graded in thickness according to the depth and consistency of the growth, gradually lessening the thickness at the outer edges, using great care and design to have as much symmetry as possible, leaving a cleanly cut edge. After this is applied, he cuts a piece of lint the exact size of the area to be covered. Just beyond the lint on the healthy tissue he applies a heavy petroleum product. Then he surrounds the application with a quantity of absorbent material sufficient to catch and hold the watery elements that will be attracted by the hygroscopic qualities of the escharotic, and which, if not prevented, will cause the escharotic to gravitate and

destroy tissue wherever it reaches. This application will do its full work in from fifteen minutes to five hours, varying according to the nature and size of the growth and resistance of the skin of different patients. During the time that this application is in place the patient should be kept very quiet, particularly so in extensive growths, such as those of the breast.

The following day the writer makes an application of the **zinc chloride** in exactly the same manner in which he applied the potassium, except that he does not extend the zinc to a point of contact with the healthy or undestroyed skin. If the application is thus made with care there will be absolutely no pain resulting from it, the patient remaining perfectly comfortable. This application penetrates the first completely; also hardens and contracts the eschar made by the potassium, causing more or less tension on the edges according to the extent of the growth; this traction causes inconvenience, not pain, and is probably the condition which has characterized escharotic treatments as drawing plasters. The eschar thus produced exfoliates in from four to twenty-one days, varying in each individual case leaving a smooth and perfectly healthy granulating surface, absolutely bloodless, and perfectly free from any obscuring elements. Brown (Med. Record, May 18, 1907).

Jennings, of London, in his book on "Cancer and Its Complications," states that "when caustics are employed to destroy a cancerous growth of any considerable dimensions the results are far inferior to excision or amputation under modern conditions. The bulk of the growth is hardly ever eradicated, and manifest local recurrence occurs ordinarily after the lapse of a few weeks. The caustics are applied and reapplied, and this sad treatment goes on until the patient is relieved by death of a treatment which adds pain to that of the disease, which it ordinarily aggravates."

He makes an exception in favor of caustics in certain very old and debilitated patients where there is an open ulcer, with the surrounding tissues adherent to the ribs, for the purpose of arresting offensive discharges for a while. He recommends a preparation consisting of:—

R Hydrochlorate of

cocaine 2 Gm. (30 grs.).
Caustic potash .. 6 Gm. (1½ drs.).
Vaselin 8 Gm. (2 drs.).

After the skin is well cleansed, small portions of this paste are well rubbed in with a wooden spatula, and in a few minutes considerable tissue can be destroyed. The charred portions should be carefully wiped away with absorbent cotton during the application. Albert Carson (Mass. Med. Jour., Dec., 1911).

Electro-ignition or **electrocauterization** has been used systematically in cancer by the writer for 18 years and he has been impressed with its efficacy. The lesion is left open and it is easy to apply the electrolysis anew at the slightest trace of recurrence. The eschar does not invite infection, and there is no danger of injury from radiation as with the actual cautery. He deems the combination of surgery and electro-ignition or electrocauterization ideal in all operable cases. E. Cisneros (Semana Medica, July 5, 1917).

Following salve recommended for epithelioma of the skin: 0.2 Gm. (3 grains) each of **arsenic trioxide**, **copper sulphate**, **methylene blue**, and **methyl violet**; 0.5 (7½ grains) **quinine hydrochloride**; 0.75 Gm. (12 grains) **tartar emetic**, and 1 Gm. (15 grains) each of **camphor**, **menthol**, **phenol**, and **antipyrin**. The last 4 ingredients, mixed together, deliquesce and form the vehicle for the other ingredients added in turn, leaving the methylene blue and methyl violet till the last. Two applications a week are made. De Rezende (Brazil Medica, May 11, 1918).

[See also a paper by A. R. Robinson entitled "Errors in the Treatment of Cutaneous Cancers," N. Y. Med. Jour., Dec. 29, 1906. H. H. JANEWAY.]

But most of the cases to which this form of treatment is suitable yield to **X-rays** (*vide infra*), and with much less deformity.

Liquid air and carbon dioxide snow may also be employed with advantage in proper cases and leave a very slight scar; the latter is much more readily handled and controlled, and promises to be a valuable addition to the treatment of superficial epithelioma.

Curetting has been strongly advocated in the past, and may occasionally be of value in removing superfluous diseased tissue, in conjunction with other treatment. But used alone it is seldom able to reach and remove all the morbid growth, and many recommend the subsequent use of caustics, or the free employment of the **galvanic cautery** after curettage. In small, superficial epitheliomata, however, a thorough curetting, with the subsequent filling of the cavity with powdered **pyrogallic acid**, will often give excellent results.

Medical Applications.—These, of course, can have very little curative effect on any of the forms of cancer, but it is a mistake not to appreciate their value as adjuvants, and to use them properly under certain circumstances. Mild **ichthyol ointment** is of great service in connection with the **X-ray** treatment of epithelioma, and various antiseptic and soothing applications, in the form of lotions or ointments, will often add greatly to the comfort of the patient and aid the healing process.

Peroxide of hydrogen, followed by a proper ointment, is invaluable in many ulcerating forms of cancer, where foreign micro-organisms contribute so largely to the keeping up of the production of pus.

The much vaunted treatment of carcinoma by **trypsin** is also worthy of mention, as an attempt, perhaps, in the right direction. Dr. James Beard, of Edinburgh, called attention to the fact that about the seventh week in fetal development the villi of the chorion began to disappear, synchronously with the development of the pancreas, and he assumed a connection between the two events. He further assumed that all malignant tumors represented abortive attempts of certain cells to reproduce the chorionic type of cell, and that those cells which do this are misplaced and included in other tissues during embryonal development. The correlation of these two assumptions furnishes the explanation of the action of trypsin in cancer. He then found by actual experiment that trypsin possesses a specific and destructive effect on chorionic cells.

At the Cancer Congress in Berlin, March 8, 1905, among the conclusions of a series of investigations by Blumenthal, Newberry, and others were the following: Trypsin quickly dissolves cancer-cells, while pepsin attacks them with difficulty. Cancer-cells produce an intercellular ferment, which is capable of dissolving all the tissues of the body, and is termed **malignic acid**; this ferment is neutralized by trypsin.

Unfortunately, the high hopes to which these investigations led were not confirmed by other observers at a later Cancer Congress, and, while there have been some favorable results reported, wide experience has shown that but little if anything can be expected from this method of treatment. The trypsin treatment of cancer has recently undergone a very thorough trial and investigation at the New York Skin and Cancer Hos-

pital, a trial embracing over 300 cases, with the result that in but very few instances was there found the slightest support for the treatment.

X-ray.—This method of treatment has now passed the experimental stage, and most observers are pretty well agreed upon the limits of its field of usefulness, though some are still extravagant in their claims as to its value.

It must first be remembered that the X-ray is a double-edged tool, which, while capable of effecting very great good, is also capable of inflicting harm, both to the patient and the operator. But this latter need not at all deter one from using it when it is rightly indicated, for, while there have been a few sad examples of serious damage to the operator, these have mainly occurred early in the practice, and before the dangers were fully appreciated, and on the other hand there are thousands of operators who have manipulated it daily for years without harm. Also in regard to any harm to the patient, there is practically no danger with a careful and skilled operator, and the relatively few instances of burns inflicted upon patients by it are insignificant when compared to the thousands of applications which have been given with the greatest benefit. Space does not permit the expansion of this subject fully treated of elsewhere, but it will readily be understood that success in the use of the X-ray depends very largely upon the knowledge, experience, and care of the operator; it is not enough simply to apply the X-ray; it must be rightly employed to be effective.

It is next to be remembered that the value of the X-ray is relatively limited

in cancer, and that the lines of its usefulness have been pretty clearly determined, so that it is unwise to waste time in its employment in wrong directions. We will first mention that class of patients in which it has been found to be pre-eminently of service, and then consider the class on which it is less useful or useless.

The treatment by X-ray finds its most promising field of operation in the superficial, basilar-cell epithelioma about the face, and in this the results are commonly most gratifying, the lesion melting away and often leaving a hardly perceptible scar. This method of treatment in suitable instances has proven a boon indeed when compared with the previous unsatisfactory methods of dealing with certain of these cases. Sufficient time has now elapsed to allow of a fair judgment in regard to the permanency of the results of this form of treatment. Pusey reports 72 per cent. of successful cases remaining well after a period of three years or more, and the experience of many others confirms this; indeed, in properly selected cases, when judiciously used, this method of treatment can give even a much larger percentage of cures, and when efficiently used, and for a long enough time, the ultimate results are most satisfactory.

Many have also reported that the X-ray is of value in connection with the surgical removal of cancer, and that its postoperative use will prevent the recurrence of the disease. In recurrent and non-operable cancer the proper employment of the X-ray is often of service in relieving pain and in improving the condition of the ulceration, and it has been claimed by good observers that in the latter instances the disease has been checked. But, as has

been stated, the power of the X-ray, as thus far developed, is limited, and the experience of many shows that it has relatively little effect in deep cancer.

Most observers agree that the X-ray should not be used in cancer of the lower lip, tongue, or throat, nor in cancer of the breast, uterus, or penis; the reason probably is that the blood-supply is so excessive that the operation of the ray is interfered with, for we know that in the use of the Finsen light in the treatment of lupus the part must be kept exsanguinated by constant pressure with the lens.

Practically, therefore, the X-ray is limited in the treatment of cancer to the superficial forms of epithelioma, and especially to those about the face; some have reported good results in Paget's disease of the breast, but most observers advise against it.

The type of epithelioma giving the best results is the basal cell epithelioma. In the writer's opinion, practically every case of this kind can be cured by the X-ray treatment. In certain cases showing extensive tissue change, he prefers to supplement it with methods to remove much of the diseased tissue, such as **electrocoagulation**. Squamous cell epitheliomata are cured with greater difficulty, and a most guarded prognosis should be given. If for any reason electrocoagulation can not be applied in epitheliomata, preceding the X-ray therapy, excision is indicated. If metastasis has already taken place, the involved glands should be removed surgically.

Degenerating moles should be removed either by **desiccation**, **electrocoagulation** or **excision**. The writer prefers desiccation or electrocoagulation. The necessity for wide excision and complete removal is urged. Following the removal, a single full dose of deep röntgentherapy should be given, and usually this is sufficient. The limitations of röntgen treatment

of deep-seated malignant disease are great. Apparent cures of deep-seated malignancy under X-ray therapy alone have been noted, but the number of cases is too small to justify its recommendation to the exclusion of operative procedure. G. E. Pfahler (*Jour. Amer. Med. Assoc.*, lxi, 985, 1917).

During X-ray treatment one must guard against toxemia or acidosis. It is best to give alkalis in large doses before or after massive radiation. Care must be observed in the filtration of the secondary rays, and not less than 3 millimeters of aluminum and $\frac{1}{4}$ inch of sole leather used. Frequent urinalyses, blood-pressure readings and blood examinations should be made, and during the treatments the room should be carefully ventilated. By perfected technique the number of burns has been reduced. The patient must be protected with coverings impervious to the ray and the dosage carefully regulated. The Coolidge tube permits the emission of great quantities of röntgen rays. R. B. Armstrong (*Journal-Lancet*, xxxviii, 190, 1918).

In nevocarcinoma or melanosarcoma, starting in imprudently irritated nevi or beauty spots, dangerous through lymphatic and visceral metastases, and met with even in young subjects, X-ray treatment is useless and should be replaced by **surgery** or **electrolysis**. Small skin tumors secondary to cancer, *e.g.*, of the breast, frequently disappear under the rays, but the prognosis of the underlying disease is not in the least improved. In all skin cancers an early diagnosis of the type of cell present, basocellular or spinocellular, should be made, by histological examination if necessary, and the treatment at once adjusted accordingly. J. Darier (*Bull. de l'Acad. de méd.*, June 4, 1918).

In England, J. J. Thomson (*Brit. Med. Jour.*, 1910, ii, 512) has suggested the use of **secondary rays** in order to produce an effect in deep-

lying tissues. The secondary rays are to be excited by a primary ray of known penetration power from metals with which the tumor tissue is injected. Thus far, however, only unsuccessful attempts have resulted.

Radium.—Since the establishment of the Radium Institute in Paris much work with radium has been done, and Wickham and others have reported some remarkable results in a variety of cases, including epithelioma.

Wickham's work at the Paris Institute includes some remarkable observations in cancer of the breast, which, if confirmed, is of the greatest importance, going to show that even deep-seated neoplasms can be reached by these radiations when used in a particular manner, the details of which cannot be entered upon here. It may be stated, however, that by means of metal shields and other coverings he varies the activity of the radium, and for deep tumors he secures only the hard *beta* and the *gamma* rays, which penetrate deeply and which are made to act on the disease for many hours daily. Also by an ingenious contrivance he makes several applications at once around the tumor, the radiations crossing and recrossing one another. Here, again, the method and skill of employing the remedy have everything to do with results.

Wickham reports (Brit. Med. Jour., 1909, ii, 1748) 600 cases of cancer treated by radium during the preceding five years. He concludes that radium influences only the limited and accessible growths. It can improve a primary tumor when metastases are present and make the patient more comfortable by diminishing the bleeding discharge and pain. Exceptionally it can transform

an inoperable growth into an operable one.

The writer urges the importance of radium in the cure of Röntgen-ray cancer. It is only in the advanced stage of the latter that radium is not beneficial. His first case so treated was in 1903, and 1 application of radium cured the epithelioma. The great advantage in the radium treatment is that it can be applied in many situations not accessible to freezing, and its relative freedom from pain. Robert Abbe (Jour. Amer. Med. Assoc., July 17, 1915).

For the last 3 years the writer has been testing the therapeutic action of radium on cancer at the Memorial Hospital, approximately 425 patients being treated for cancer of almost every portion of the body and in all stages. Certain conclusions may tentatively be drawn, chief among which is that radium may be regarded as one of the most efficient remedies, particularly for the cutaneous epitheliomas. Two forms of malignant tumors were so susceptible to it that it became the treatment of choice, viz., the cellular carcinomas originating in the testicle or ovary, and the lymphosarcomas, particularly in the early stages. Almost specifically benefited also were the myelogenous leucemias with enlarged spleens, a single application causing the splenic tumor to disappear with an accompanying reduction in the white blood count.

Of the 425 cancer cases treated all were malignant except 2; 120 showed complete retrogression, 110 being known to be free from the disease; of these 66 were cutaneous, so that 44 represented complete retrogressions of the more malignant forms of cancer. Of the other cases 129 had improved; 55 were still under treatment and 162 had not improved. A study of the clinical records developed the fact that the favorable character of the end result was invariably proportional to the age of the tumor treated. Practically all

the patients in both the unimproved and improved group had advanced growths when treatment was begun. While only those patients remaining well after a 3 to 5 year interval may be deemed cured, nevertheless the character of many of the retrogressions observed bore the stamp of sufficient permanency to warrant the use of radium in early cases with the advantage of offering an escape from operation. H. H. Janeway (Trans. N. Y. Acad. of Med.; N. Y. Med. Jour., Sept. 8, 1917).

In a collective report of 642 cases of cancer and allied conditions treated by radium at the Huntington Hospital of Harvard University, the writers conclude that many cases of advanced, inoperable or recurrent cancer may be given benefit by treatment with radium. In such cases the relief may include one or more of the following advantages: relief of pain, diminution of discharge, less offensive discharges, relief of hemorrhage, diminution in the size of tumor masses, even to their total disappearance; and improvement in the general condition of the patient. To these must be added the undoubtedly beneficial psychic effect upon the patient. In a very small number of advanced and apparently inoperable cases, improvement may occur such as to permit a radical operation to be performed. Of the 642 cases, 354 or 55 per cent. received definite benefit.

In a certain proportion of cases of superficial non-metastasizing types of cancer (about 35 per cent.) and in a much smaller number of cases of metastasizing cancer, radium is capable of destroying the clinical manifestations of the disease. In a limited number, recurrence after apparent destruction of the lesion has taken place. In certain situations, as on the eyelids, radium treatment of lesions is to be preferred to operation.

In keratoses, papilloma and other benign skin diseases regarded as precancerous, radium is effective in

destroying the clinical manifestations of the disease in from 48 to 60 per cent. of cases.

In myelogenous leucemia, the beneficial effects of radium are pronounced, and although recurrence of symptoms may take place, the clinical advantages of radium therapy are very marked.

In malignant lymphoma, lymphosarcoma, and Hodgkin's disease, the lesions appear to be especially sensitive to radiation, and definite though temporary benefit is obtained. When in accessible situations, it would appear that the disease can be controlled by radiation for a considerable period of time.

In the treatment of many other tumors and diseases radium has been used with benefit, depending largely upon the extent of the disease, its depth in the tissues, and the practical ability to apply sufficient radiation to modify or destroy tissue or tumor growth. Among the conditions in which radium treatment has proved of special value may be mentioned: recurrent or inoperable carcinoma of the cervix or of the body of the uterus, Hodgkin's disease and malignant lymphoma, myelogenous leucemia, inoperable squamous cell carcinoma of the tongue, jaw and buccal mucous membranes, in non-metastasizing epidermoid cancer and in the more benign lesions of keratoses, papilloma, and other so-called precancerous conditions.

Radium therapy has proved so far to be of little benefit in recurrent carcinoma of the breast, carcinoma of the stomach and intestine, carcinoma of the glands of the neck by extension from cancer of the tongue, mouth and lip, and in general in deeply seated metastatic extension of cancer from any region. Duane and Greenough (Boston Med. and Surg. Jour., Dec. 6, 1917).

The writer reviews the results of treatment of 1015 cancer patients with radium often in conjunction with the Röntgen rays. In 207 cases of deeply rooted inoperable cancer

in different organs, primary or recurrence, a clinical cure was realized in 14; 35 were permanently improved, and 86 failed to be benefited. Forssell (Hospitalltid., Mar. 21, 1917).

Comparison of the relative merits of **radium** and **X-rays** in the following table:

RADIUM.	X-RAYS.
Has more penetrating rays in smaller volume.	Have less penetrating rays in greater volume.
Easier to handle.	Technique very exacting.
Applicators small in size.	Apparatus large and heavy.
Portable.	Practically non-portable.
No danger of high tension electrical shocks to patient.	Patient must be protected from high tension shocks.
Can be used in cavities.	Use in cavities has been abandoned.
Effects easily confined to small areas.	Larger areas can be treated.
Treatment takes more time—average treatment four hours per area.	Treatment takes less time—average treatment five minutes per area.

In the author's opinion the most efficient treatment of cancer is based on: The education of patients, to the end that they will come for examination early; the maximum safe erythema dose of radium or X-rays on the day previous to operation; radical operation; and postoperative prophylactic X-ray or radium treatments. A. F. Holding (Amer. Jour. Röntgenol., vii, 306, 1920).

Incision of a primary malignant lesion and block dissection of metastatic glands is not sufficient. Migratory cells in lymphatic ducts must also be taken into consideration, else they will drain into the tissues after the glands are removed, with rapid progress of the disease as result. At least 1 maximum **radium** treatment with accurate technique is advocated, preparatory to any other procedure. At least 3 radium treatments, averaging 6 weeks apart, should also follow any operative procedure. The wisdom of ante- and post-operative radium treatment is amply demonstrated by clinical evidence. The invaded glands not broken down usually disappear. If degenerated internally, however, they do not disappear, but radium treatment converts the capsule into benign fibrous tissue. Then the gland can

be incised and drained with safety. The author uses hollow, non-corrosive, steel **needles, containing radium** in known quantity. These are inserted into malignant growths and glands, producing results that cannot be produced by radium applied outside in capsules or plaques. The judicious combined use of operative surgery, electrothermic methods, radium, and the X-ray often clinically cure even very advanced and inoperable cases of carcinoma and sarcoma. W. L. Clark (Trans. Phila. State Med. Soc.; Rec., Jan. 1, 1921).

The use of the other radioactive substances such as **actinium** and **mesothorium** in the treatment of cancer has been attended by an indifferent degree of success.

Finsen Light.—Early in the use of this remedy it was thought that it would be able to reach deep-seated neoplasms, so marvelous were the results obtained by its use in lupus. But experience has shown that its powers are very limited, and, although with very careful manipulation superficial epithelioma may be overcome by it, it is powerless to favorably affect lesions which are at all deeply seated.

Leucodescent Lamp.—Much the same may be said in regard to the leucodescent lamp, which has been tried and found wanting. It is questionable if it has any value as a curative agent even in the superficial forms of cancer, or in the ulcerations of deeper forms, but the heat given off will often be of value in alleviating the pain of ulcerating lesions; it is rapidly going out of use.

Fulguration Treatment.—This newest addition to the non-surgical treatment of cancer seems to have something of promise in it, although already some are skeptical as to the real value which has been claimed for

its use. It is in reality only the employment in an exaggerated degree of what has for some time been found of value in certain other conditions, namely, a very strong high-frequency current, in a manner proposed by Keating Hart, of Marseilles. Space does not permit a full presentation of the method of its employment, but some data may be given, as further developed by Czerny. The patient being under an anesthetic, the most intense brush discharges are given from a metal electrode at a distance of from $\frac{3}{4}$ to $1\frac{1}{2}$ (by some; 5 to 6 in. by Dr. Keating Hart) inches, and for from five to forty minutes. After this the cancerous part is removed by the knife or a sharp spoon, and the wound is exposed again to fulguration, to kill any remaining cancerous cells. A destruction of tissue is effected for hardly half an inch beneath the surface, so that in large growths a preliminary removal by the knife or curette is recommended. Keating Hart maintains that the high-frequency spark possesses a special predilection for the cancer-cells, even to the extent of reaching metastases in regionally enlarged lymph-nodes.

In Czerny's opinion there is breaking up of the cancer-cells, which have much less resisting power than healthy tissue-cells. In addition to the special destructive action upon the carcinomatous elements, the spark produces stimulant effects upon the connective tissue surrounding the cancer-cells; by this means granulations quickly spring up and healing of the ulcer proceeds rapidly.

The treatment has not been in use long enough to properly estimate its value. Keating Hart has reported a healing of 95 per cent. of cancer of

the skin, 40 to 50 per cent. of cancers of the breast, and 20 to 25 per cent. of cancers of the mucous membrane. Czerny in two articles has reported the treatment of 59 patients by this means, with cancer in various locations, internal and external, and with a fair measure of success. As a result of his experience he draws the following conclusions: Fulguration will cure superficial, soft, cancerous ulcerations, and stimulate healthy granulation to a marked degree. It is more certain and quick than the Röntgen rays, and must be considered as an important subsidiary means in the treatment of cancer. In indurated and more deeply infiltrated carcinoma a previous excision of the growth must be performed; in deep-seated cancer fulguration finds a very limited sphere of utility. In inoperable and recurrent cancer fulguration can successfully affect the itching, bleeding, and pain, and by this means prolong the life of the patient and diminish discomfort.

It is hardly fair to fulguration to accept Czerny's conclusions and explanation of its action; de Keating Hart does not consider fulguration to be a caustic or to effect a cure by destruction of tissue. He believes its action is rather upon the healthy tissues, creating a reaction unfavorable to the growth of cancer; de Keating Hart has told the author that he considers Czerny technique faulty, as also that of many other surgeons. He further believes that fulguration is a powerful adjuvant to the X-rays, together with heat, sensitizing the cancer cells to the influence of the X-rays.

[S. Imbach (Schweiz. Rundschau für Med., No. 31, 1910) reports the use of fulguration in 32 patients, 13 of which were carcinoma and 5 sarcoma, the remaining 14 being other affections; 19 patients were

healed; 8 were treated with no results; 1 patient, however, of 55 years, with a twice-recurrent cancer of the face the size of a fist, was healed and was still well at the time of the report, seventeen months later. H. H. JANEWAY.]

Much work has been done at Czerny Institute upon the combined treatment of cancer by several of the methods depending upon the use of physical agents.

Werner and Caan (Münch. med. Woch., 1911, lviii, 1225) have given their results by such methods in 253 cases. They conclude that the treatment by the **combined high-frequency current** and **X-rays** diminishes the susceptibility of the normal tissues to X-rays, but increases the susceptibility of tumor tissue to them. Deep tumors should be exposed by operation in order to obtain the greatest effect.

Czerny (Münch. med. Woch., 1911, lviii, 1897) has seen tumors otherwise excluded from any therapy melt away by the use of radium and X-rays. Chemotherapeusis and immunization support the organism in its fight against cancer. Many sarcomas show themselves peculiarly susceptible to such measures. Many deforming operations are prevented, and the frequency of recurrences after operation diminished. There are many possibilities which indicate the morning of a better future.

Other observers have more or less confirmed the claims which have been made for fulguration, or the use of the powerful high-frequency current in cancer, but the most sanguine observer can hardly look upon it other than as an adjuvant applicable in certain few cases. From what we know, however, from experience along certain other lines, especially in dermatology, the

high-frequency current does have a peculiar effect on living tissue, and it is possible that further observation may demonstrate that it has some real control over the aberration in the action of tissue-cells which we call cancer.

It has been found that **electrothermic methods** of treatment of cutaneous cancer were more uniformly reliable than other procedures; this is also true of cancer of the lower lip and oral cavity; but, **operative surgery, X-ray, or radium** may be used to advantage when metastasis has occurred. When glands or large blood-vessels are involved **electrothermic methods** could not be used with safety in the region of the blood-vessels. Operative surgery and X-ray were usually preferred in mammary cancer, but a breast might be removed by electrothermic methods. Operative surgery, radium, or both in combination, ordinarily seems best in cancer of uterine cervix, but electrothermic methods are also of value. Cancer of bladder and rectum, unless seen very early, hopeless. If seen early, electrothermic methods offer the best chance of success. Electrothermic methods are successful when the disease is localized and have the advantage over other methods in that the diseased tissue is entirely destroyed with one treatment, blood and lymph channels being sealed, and superior cosmetic results obtained. The successful treatment of cancer, generally speaking, means the intelligent use of the methods best suited for individual case; or, when indicated, the use of combined methods. W. L. Clark (Trans. Phila. Co. Med. Soc.; N. Y. Med. Jour., Apr. 6, 1918).

Sera and Vaccines.—The treatment of cancer by **sera** is based upon the assumption that immunity of some kind can be created against cancer.

There are many facts which warrant such a view and considerable evidence, which is to be found in experimental cancer among animals.

An active immunity exists against the successful inoculation of cancer of one animal into another of a different species, and a certain degree of active immunity against the successful inoculation of cancer from one animal into another of the same species, but of slightly different variety. V. Leyden has found that the tumor which Jensen discovered in mice and first described could be transplanted with ease (in 70 to 80 per cent. of the cases) into mice of Copenhagen, but could not be transplanted to Berlin mice.

Borrell ("Le problème du cancer," 1907, 41) could only transplant the same tumor in 30 to 40 per cent. of the cases in the Parisian mice. Haaland (Berl. klin. Woch., 1907, xliv, 713), working with Ehrlich on sarcoma of mice, obtained a series of takes in 97 per cent. of Berlin mice and only 24 per cent. of takes in Hamburg mice. A tumor composed of mixed sarcoma and carcinoma gave in Berlin mice a pure sarcoma and in Danish mice a pure carcinoma.

These experiments, therefore, demonstrate the existence of a varying degree of active immunity in different varieties of animals. It has been found that in both mice and dogs—indeed, in all animals—a very strong degree of active immunity exists against inoculation in those animals in which the tumors have spontaneously retrogressed.

For lymphosarcoma of dogs Sticker has found that age, location of inoculation, pregnancy, a poorly nourished condition, or organic dis-

ease has had no effect on the success of inoculation of tumor tissue.

An active immunity against the successful inoculation of a tumor may be induced in an animal. Such a condition can be accomplished by the injection into the animal of certain normal tissues, liver (Borrel), and blood of other mice or rats (Woglom, Jour. Exp. Med., 1910, xii, 29), by the injection of **splenic tissues**, of **embryonic tissues**, and finally by the **tumor tissue** which has either been killed by fragmentation or reduced in virulency by heat. The degree of active immunity thus resulting is greatest if the tissues used for the injection are closely related to the tissue from which the tumor originated; thus, it is the skin of mice embryos which is most effectual against certain epitheliomas in the mice, and hashed flayed embryos will produce no immunity against inoculation (Bashford, Murray, and Hasland).

It must be remembered, however, that animals which have been rendered in this way immune to the inoculation of tumors may later develop spontaneous tumors of their own; so that this form of immunity is a very different thing from active immunity against the growth of tumor tissue in general.

It is generally difficult to re-inoculate an animal in which a tumor is already growing, but our ability to produce in this manner an artificial metastasis depends to some extent upon how rapidly the inoculated tumor grows. If the tumor is a very rapidly growing one a second inoculation will frequently not succeed, and also frequently, if the tumor is growing poorly and certainly if it is

retrogressing, a reinoculation never succeeds. **Reinoculation** frequently succeeds in tumors of moderate or normal rate of growth. After a complete extirpation of a tumor Schöne has found in mouse carcinoma that reinoculation succeeds; on the other hand, in tumor of a moderate rapidity of growth after incomplete excisions reinoculation may be unsuccessful. These results have been confirmed in rat sarcoma by Uhlenhuth, Handel, and Steffenhagen.

A passive immunity may be induced by the **serum** of healed animals. When such serum is mixed with the cancer cells inoculation with these cells will produce a very much diminished number of takes.

But, further than this, Clowes and Baeslack (*Jour. Exp. Med.*, 1906, viii, 481) have cured 12.3 per cent. of mice with tumors by injecting such a serum. Borrel ("Le problème du cancer") has treated successfully a mouse tumor with the serum of a sheep which had been previously injected with mouse-tumor tissue.

Beebe has shown that it is possible to cure dogs with lymphosarcoma by bleeding them and transfusing them with the blood of animals in which a spontaneous retrogression of the tumor has taken place. The blood of a normal animal, though exhibiting some tendency to cure other dogs, was in no case so successful as the blood of immune animals.

Beebe has, however, shown that the blood of immune animals is not alone sufficient. It must in some way imitate a reaction in the tumor. There is also evidence to show that growing tumors are necessary at the time of transfusion in order to cause

the retrogression of the tumor. If, for instance, the transfusion is performed five days before the implantation a retrogression of the tumor implanted will not occur.

V. Dungern and Sticker (Second International Congress on Cancer, Paris, 1910), from whom most of the above facts have been collected, state that there can no longer be any doubt about the existence of immunity against transplanted tumors in mice, and, we may further add, of tissue specificity in the matter of this immunity.

Bashford (Fourth Report of the Imperial Cancer Research Fund) sums up his conclusions from the facts and his own work in the following words: "Resistance to inoculation is induced only by living cells, either cancerous cells or normal cells of the same species. Under similar conditions the cancerous cells and the normal cells of strange species are both devoid of the power to induce resistance. An animal's own tumor and its own normal tissue are devoid of this power, and the means which prevent the successful inoculation of the tumor of another individual do not prevent the successful inoculation of an animal's own tumor. Tumor tissue usually induces resistance against itself quite as well as and, with regard to the phenomenon of spontaneous healing, much more effectively than any other tumor. Furthermore, animals which have proved resistance to repeated inoculations of a tumor have subsequently developed spontaneous tumors showing progressive growth. These experimental inquiries into the production of growths by inoculation on the one hand and its prevention on the

other hand agree in demonstrating individual relations as obtaining between a tumor and the animal in which it arises."

The question next arises, What is the nature and mechanism of this immunity? Ehrlich has attempted to explain the immunity of cancer by hypothesis to which he gives the name of atrepsia. He assumes that certain specific food substances are necessary for the growth of the cancer cell or, for that matter, for any cell of the body and many protozoan organisms. Special receptors only can appropriate these specific food-stuffs, and not unlikely, at least in some instances, a specific bioceptor-complement reaction may be necessary for their appropriation; at any rate, these specific foodstuffs are present in limited amounts, and whether they are available or not for the cancer cells depends upon the relative avidity of the receptors of the cancer cells and the normal body cells for these specific foodstuffs.

Ehrlich first shows the importance of specific nutritive substances by reference to the part played by lecithin in activating the amboceptor of certain snakes' venom, and of hemoglobin in the life of influence bacilli. He then illustrates his theory by the increased acidity of certain chemoreceptors of some body cells for arsenical preparations, of fuchsin in the course of certain trypanosome infections in which the trypanosomes, although apparently hypersensitive to the arsenic, are actually more resistant to it.

Two observations upon experimental cancer lend support to this theory: First. Although mice cancer cannot be successfully inoculated into

rats, it can be kept alive in rats for several days and then removed again and planted into mice and made to grow as luxuriously as if primarily implanted within these mice. Ehrlich explains this fact by assuming that when the transfer is made into the rats enough of a specific substance necessary for the life of the graft is for a few days carried along with the graft into the rat. If the graft is left within the rat for a longer time this specific food substance becomes exhausted and the graft dies.

The second observation is the fact that our ability to cause artificial metastasis is inversely proportional to the malignancy of the tumor. Ehrlich believes that the primary tumor exhausts, by its rapidity of growth, some substance necessary for the growth of its metastases. The author does not believe, however, that the atreptic theory of immunity of tumors is entirely in accord with facts. The tendency at the present time is to accord to cancer a true antibody immunity.

As v. Dungern has shown, the persistence of immunity after the retrogression of tumor tissue could not be explained by the absence of specific foodstuffs. Second. The development of immunity when a large growth is partially excised. Third. An inoculated tumor causes counter-reactions in the organism into which it is implanted, and these may not be strong enough to prevent the growth of the first tumor, but can be strengthened by a second inoculation. Fourth. Certain reactions of an anaphylactic character are originated by the introduction of tumor cells into immune animals. These are edema

and, above all, a collection of plasma cells, lymph cells, and monophages in large numbers.

De Fano has also noticed cellular reactions in immune mice, though they have been missed in non-immune animals. V. Dungern attributes these to the action of an antigen.

Turning from the realm of experimental cancer to human cancer, one will find most of the facts in the former duplicated by the latter. There unquestionably exists both active and passive immunity in human cancer.

Vidal has given the following classification of the various methods by which it has been attempted to produce immunity in human cancer:—

Passive immunization.

I. Normal serum therapy (sera of healthy animals).

II. Serum therapy by immune sera.

Cellular serum therapy;
antigen from neoplastic
cells and their derivatives.

Natural cellular serum
therapy; serum from healed
or cancerous animals.

Artificial cellular serum
therapy (cytolytic serum).

Parasitic serotherapy.

Bacterial serum therapy.

Active immunization.

Cellular vaccines; the
cells of new growths modi-
fied or intact.

Non-bacterial serum
therapy yeasts.

Autocellular, heterocellu-
lar, and xenocellular vac-
cines.

Parasitic vaccine therapy.

Bacterial vaccine.

Bacterial toxin therapy.

Non-bacterial yeast; coc-
cidia.

Toxin of bacterial origin;
xenobacterial toxin.

Non-bacterial toxins.

All other parasites, yeasts,
and molds.

All of these methods of producing immunity in a patient suffering with cancer for the purpose of curing the disease have been tried with a greater or less degree of claimed success. Some of the methods have been attended with considerable success and encourage the view that cancer will ultimately be cured along these lines.

Representing the auto- and hetero-cellular **vaccines** numerous attempts have been made to produce immunity by the injection of comminuted or ground-up cells of the patient's own tumor or of another tumor of similar histological structure or of extracts of these tumors. In some instances a remarkable success has attended such trials. The most noted paper upon

Autocellular serum (pa-
tient's serum; antigen from
tumor or from same pa-
tient); healed cellular serum
(serum of healed animals).

Cytolytic xenocellular se-
rum (cytolytic serum; etio-
logical cellular serum; an-
tigen from histologically
allied cells, epithelioma,
sarcoma).

Bacterial serum (etiologi-
cal) derived from (antigen)
pretended cancer bacteria;
antigen derived from bac-
teria not etiologically re-
lated to cancer.

All parasites from indif-
ferent (etiological) sources.

Tumor of same patient;
tumor of another species of
animal; material foreign to
the neoplasm.

Any bacterial vaccine
(bacteria pretending to be
the cause of cancer); xeno-
bacterial vaccine (non-can-
cerous bacteria; streptococ-
cus).

All foreign bacteria.

Toxin of cancer bacteria;
toxin of non-cancerous bac-
teria.

this subject is by Coca and Gilman (Philippine Jour. of Science, B, 1909, iv, 391).

The vaccine treatment of cancer has given a number of surprising results. The writer has seen a large sarcoma of the neck apparently healed by the injections of autogenous vaccines.

The most favorable report of this method of treatment, as has been mentioned, is by Coca and Gilman. These authors have observed some very remarkable results which cannot be neglected even though the subsequent work of the same writers has not confirmed their first results. They prepared a suspension of the finely divided tumor in normal salt solution and alcohol, to which a small quantity of carbolic acid was added as a preservative. The patients were injected with this material. None of them showed any ill consequences. Three of the patients who possessed inoperable growths showed marked improvement, the growth softening and disappearing. Fourteen of the patients were subjected to operations, most, but not all, of the tumor being removed. After seven or eight months no recurrence took place. One patient showed a recurrence which was attributed to too large a content of carbolic acid in the vaccine. All the tumors treated were of the epithelial or glandular variety. No sarcomas were treated. No serious effects, but rather beneficial ones, followed the absorption of the broken-down tumor tissue.

Although Coca and Gilman's results have not been repeated by others, they are yet important because they indicate some impression on carcinoma by agents of this class.

(See also the article on BACTERIAL VACCINES in the present volume.)

Hodenpyl (Med. Record, 1910, lxxvii, 359) has made the attempt possibly based upon another principle to cure carcinoma by the injections of **ascitic fluids** from cases of carcinoma, but particularly from cases in which the cancer has shown retrogression.

Concerning the use of **xenocellular vaccines** attempts have been made by Braunstein (Berlin. klin. Woch., 1911, xlviii, 2029) to treat human cancer with the injection of **splenic pulp**. Thus far his report deals only with experiments on animals affected with sarcoma. These have been very successful. He promised to report his results on the human later.

R. Oestreich (Zeitschr. f. Krebsforsch., 1911, xi, 44), noticing that cartilage and the tissues of the arterial walls are rarely attacked with cancer, and that these tissues are rich in **chondroitin sulphate of sodium**, has attempted to cure cancer by injecting the latter substance under the name of antitumin. He used the remedy subcutaneously. Sections from the treated cases, all late cases of cancer, show considerable necrosis and leucocytic infiltration and a marked clinical reaction.

In line with the suggestion furnished by animal experimentation, and also suggested by the rarity of cancer in the young, Fichera (Polislinico, 1910, xvii; Sez. prat., 845) has treated cancer by the injection of **autolysates of human fetuses**. The hashed tissues are mixed with 20 parts of physiological salt solution, to which a little thymol or phenol is added. This mixture is covered on top with toluol and kept at 37° for two months. The suspension is then

tested for its sterility and injected in quantities of 2 to 3 c.c. two to four times a week.

He has treated in this manner 36 cases of inoperable cancer. Only 18 of these were given a thorough course. Eight of the patients did not seem to be benefited, but in 10 others a favorable influence was unmistakable. In 5 patients the malignant new growths entirely disappeared. Of the 5 cases the cancer was in the breast in 3, and in the thyroid in 1, and rectum in the other.

The effect of **homogeneous products of fetal autolysis** in cases of malignant tumors in the human subject is further reported on by Fichera. The observations, begun early in September, 1909, and continued without interruption, have been all conducted on inoperable cases, of which only 7 had received no surgical treatment; 29 had been operated on, even repeatedly, including recurrent cases and several with multiple and voluminous metastases. In each case the histological diagnosis was confirmed without exception and the clinical evolution was followed up, both anatomically and microscopically, by means of the excision of small portions, repeated even eight times. The number of patients submitted to the injections was 36. Of these, 14 stopped the treatment early by their own desire for various personal reasons, having received from 3 to 10 injections. In 4 of the other 22 cases the treatment has been only recently begun. Of the remaining 18 patients, 8 have derived no marked benefit, except in a few cases some delay in the progress of the tumor or an initial improvement of the general condition, but only to be followed by a progressive deterioration, so that in 3 of these cases a fatal result occurred. As for the other 10 cases, the beneficial effects are evident; and while in 5 cases the treatment is still proceeding, because the

tumors have neither disappeared nor become modified in structure, in the other 5 cases the neoplastic tissues have completely disappeared, or in the residual tissue repeated excisions have demonstrated the complete transition of neoplastic into sclerotic connective tissue. Of these, 3 presented metastases which had degenerated sooner than the primary tumor in a manner analogous to that observed in 4 other cases in which the glandular metastases have now disappeared, although the original tumor, or its reproduction, still exists, more or less modified. Fichera (Jour. Amer. Med. Assoc., from Lancet, Oct. 28, 1911).

Although, for the present at least, **parasitic vaccine therapy** and **bacterial toxin therapy** are not entitled to serious consideration, with the exception of Coley's attempts with the mixed toxins of the streptococcus and *Bacillus prodigiosus*, yet brief mention will be made of Otto Schmidt's **cancroidin** or **antimeristem**. Schmidt (Zentralbl. f. Bakt., Orig., 1909, 52, 11) considers that he has discovered in his mucorracemus the cause of cancer. Injections of pure cultures of his organism have caused, he believes, malignant tumors in animals, and the injection of killed cultures has cured sarcomatous rats. He reports (Central. f. Gynäkol., 1911, xxxv, 1711) several cures without recurrences in women suffering from uterine cancer. Jensen (Deut. med. Woch., 1910, xxxvi, 758) has reported a case of carcinoma of the tongue in which an enlarged gland was present beneath the angle of the jaw, and which was completely healed in one-half year's time by the use of **antimeristem**. Arsonsohn (Zeitschr. f. Krebs., 1910, ix, 367) reports 2 cases of laryngeal cancer cured by Schmidt's method. Others, however, have had no success

with the method. Beresnogowsky, for instance, has made a report of (Zeitschr. f. Krebs., 1910, ix, 373) two cancers of the breast and another of the larynx which showed absolutely no change with this treatment.

One of the most interesting methods of treatment is that which resulted from observing the disappearance of sarcoma after an intercurrent attack of erysipelas. This led to the treatment of certain forms of sarcoma by the **mixed toxins of the streptococcus of erysipelas** and **Bacillus prodigiosus**, with which the name of Coley is inseparably connected, and which certainly demands attention; although the success following its use by others does not equal that reported by him. In a classical article he reports the treatment of 71 cases by this method; of these, 40 were in patients treated three or more years previously. Of these 40 cases, 10 were not traced, but of the 30 remaining (including one case in which the diagnosis was doubtful) 10 have been regarded as permanently cured; another case remained well for five years, and then died of general metastases. Two of the cases had inoperable sarcoma of the femur, one of which was periosteal; in another case there was an incomplete operation on the head of the femur; the mixed toxins were then used, and a permanent cure of nine years resulted.

Coley stated (1910) that he had had 40 per cent. of successes in 37 cases of inoperable sarcoma. The tumors disappeared under the use of the injections of the mixed toxins of erysipelas and *Bacillus prodigiosus*.

The 2 dangers which deserve consideration are, the danger of death from collapse from too large an initial dose and the danger of nephritis from long continued treatment with

very large doses. Out of nearly 1000 cases only 3 deaths occurred during treatment and in 3 other cases nephritis developed, so the danger might be said to be negligible.

There are 5 indications for the use of the toxins: 1, in practically all cases of inoperable sarcoma; 2, before operation in sarcoma of the long bones; 3, immediately following incomplete operations in which part of the tumor could not be removed; 4, in combination with radium or X-rays, and, 5, after all operations for sarcoma and carcinoma in the hope of preventing recurrence. In addition possibly also toxins should be used in certain cases of inoperable carcinoma, though this was experimental; nevertheless, a few good results had been obtained. In the series of 1000 cases, the disease apparently disappeared in 97; 74 remaining well and free from recurrence from 1 to 24 years; 66 from 3 to 24 years, and 13 from 15 to 24 years. The greatest success was obtained with the toxins in sarcoma of the long bones and lymphosarcoma. W. B. Coley (Trans. N. Y. Acad. of Med.; N. Y. Med. Jour., Sept. 8, 1917).

Turning now to the attempts to heal cancer by the use of methods transferring **passive immunity**, one will find that the field is by no means barren of results, but rather to our mind indicating a future scientific cure of cancer.

Very little of value has been accomplished by the use of normal sera. Aside perhaps from a few rodent ulcers of the skin no actual cure has been accomplished. Some cases of cancer have been benefited, judged from the clinical symptoms. The evidence of this improvement has limited itself to a diminution of the pain, hemorrhages, and discharge and a diminution to a greater or less degree in size of the tumor, some-

times a cicatrization of ulcers of various sizes, and, finally, an influence upon the general condition of the patient. Then, only too rapidly, a cessation of the improvement and an unimpeded progress of the malignant new growth.

Hodenpyl's late efforts, which have attracted considerable attention in this country, should be classed in this category. He obtained an **ascitic fluid** from a patient with a **retrogressing cancer**; a most favorable effect was noticed upon human beings with cancer injected with this fluid. He treated altogether 47 patients, almost all of whom were distinctly unfavorable ones; considerable improvement was obtained in many of them. Due to Hodenpyl's most unfortunate death, his preliminary report was the only one published, and the promised details have, therefore, never been given to the profession.

This preliminary report, however, concluded with the following statement, which deserves quotation in full:—

"It is not my purpose to announce at this time a new cure for cancer, but to call attention to the remarkable selective necrotizing effects upon carcinoma cells of the ascitic fluid from a recovered case of carcinoma, wherever in the body of the patient this fluid is introduced. The nature and significance and the practical importance of the substances contained in this fluid and the ultimate value of this method of treatment of carcinoma are to be finally determined only by a continuance and completion of the various correlated series of investigations, chemical and biological, now under way, or by such tests as other observers may under-

take." Hodenpyl's work is exceedingly difficult to repeat on account of the difficulty of securing patients with retrogressing tumors. The injection of a simple ascitic fluid in patients with advancing cancer has given practically no beneficial results.

Following this report many attempts were made to cure cancer by the use of serum from cancerous patients. The rarity of patients with retrogressing tumors has prevented the exact repetition of Hodenpyl's experiments. Attempts with serum from patients with advancing growths have been barren of results. Hodenpyl's work should, however, be born in mind, as cases with retrogressing malignant new growths are met with from time to time. Mackay (Brit. Med. Jour., 1907, ii, 138) has collected 50 authentic cases of a more or less complete spontaneous retrogression of cancer growths. Risley (Boston Med. and Surg. Jour., 1911, clxv, 127) has reported 10 cancerous patients treated with fluids from non-cancerous patients and 45 cancerous subjects treated with serum from other cancerous cases.

No change was noted in any of the 10 patients treated with sera from non-cancerous subjects except a case treated with **spermatocele fluid**, which agent seemed to exert a marked stimulant effect upon the growth. In practically all of the 45 patients treated with the serum from cancerous subjects, there was some local or general reaction which speaks for the specificity of the fluid. In 5 cases there was a decrease or absolute abolition of the pain previously complained of. In 3 there was a decided increase in the discharge, and a moderate increase in the discharge was noted in every

patient treated. A cessation of bleeding occurred in several cases of uterine cancer. In 2 cases there was an increase in the pain. An apparent retardation of the growth occurred in 8 cases for a period of two to five months; 12 patients remained in excellent condition, gaining strength and weight during the treatment. In no case was there an actual shrinkage in the tumor.

Passing to the consideration of the artificial cellular serum therapy and the various **cytolytic sera**, a number of definite real results are on record which should encourage the hope that the way to the scientific treatment of cancer has been inaugurated. Nee in 1895 first laid the foundations of humeral reactions and of the creation of cytolytic antibodies.

At a later day v. Dungern took up the work and first showed the very great specificity of cytolsins. The intenseness of this characteristic almost led to an abandonment of these methods.

Then, Richet and Héricourt took up the work with cytolsins obtained by injections of dogs and donkeys with macerated tumor tissue, together with his immediate followers. In 1906 there had been 120 experiments of this kind upon human cancer. Their results were a varying degree of softening and reduction in size of the growth, a diminution of pain and edema, and a definite cicatrization were obtained. In some cases hemorrhages ceased and discharge lessened, and in most cases marked improvement in the general condition resulted.

These partial results have stimulated efforts to improve the technique. Cimino, noticing the leucocytic action of cytolytic serums, has attempted to

improve their action by alternately injecting animals with the macerated cancer and cultures of streptococcus. He has made 61 experiments with 7 fairly satisfactory results.

Along with this work animal experiments previously referred to by v. Dungern, Jenson, Ehrlich and Michaelis, Blumenthal and v. Leyden, Borrel and Bride, Bashford, Murray and Kramer, Uhlenhuth, and others have confirmed the belief that specific antibodies exist, and the great problem which lies before the world is, How may their efficiency be increased?

Vidal has taken up the work in a seemingly thoroughly systematic manner. He finds, in the first place, applying the Bordet-Gengou method, that two substances are concerned in the action of a specific cytolytic serum developed in a dog by injecting the same with human epithelioma, one comparable to fixateur, or amboceptor, thermostabile, and the other comparable to complement and thermolabile.

Secondly, studying the causes which influence the action of the epithelial serums in respect to the specific antibody, that there are 4 important factors: 1. The number of the injections of the antigens into the blood of the serum-furnishing animal. 2. The physicochemical condition of the antigen which the animal receives and its mode of preparation. 3. The biological condition of the antigen cell. 4. Artificial modification of the leucocytic function of the animal undergoing treatment. Concerning the first of these factors the optimum conditions oscillate about nine injections.

The following classification represents the various physicochemical

conditions in which the antigen may be obtained:—

- A. Chemically normal cells. I. Absolutely fresh emulsions.
 - 1. By glycerin.
 - 2. Preserved emulsions by some antiseptic, as chloroform.
 - 3. In a secondary state.
- B. Tissues physically somewhat disintegrated, as by freezing.
 - Normal albumins:—
 - (a) Soluble in water.
 - (b) Nucleoproteids.
- C. Antigens reinforced (or not) by a fraction of cellular albumins.
 - Albumins chemically modified:—
 - (c) Peptones.
 - (d) Nucleins.

Other things being equal, the employment of fresh emulsions has given the best results.

The biological state of the antigen cell may be influenced. It can be sensitized so that instead of 9 injections into the antibody-furnishing animal 3 to 5 will cause as many fixateurs, or amboceptors. This can be accomplished by administering it in an exactly corresponding antiserum.

The potency of the effect of the antibody is heightened by preceding the injection of the antigen by six hours with the injection of some leucotoxin of such a character that a maximum leucocytosis exists at the time of the injections of the antigen. The most efficacious leucotoxin has been found to be a combination of iodine and nucleic acid. The increase in the number of fixateurs by the use of this agent has amounted to 120 per cent.

To sum up, the following factors should be observed in the preparation of the antibody: 1. The employment as antigen of a very fresh emulsion of malignant cells, but sensitization

in an exactly corresponding antiserum. 2. An injection of a rabbit-dog serum toxic for white cells preceding the injection of the antigen by at least six hours. 3. Reduction of the number of antigen injections to solely three. 4. The blood of the animal used for the production of the antibody to be drawn at the height of leucocytosis.

One other factor of very great importance requires mention. This concerns the slow development in the blood of the treated patients of an antisensibilizing substance, which accounts probably for the loss in power of the specific cytolytic serum so often observed in the serum therapy of cancer. It is possible that it is precisely similar to the refractory states encountered in immunization against bacteria and to antianaphylaxis. At any rate, very direct proof of the presence of these anti-antibodies exists. If the tumor cells from the periphery of a neoplasm of a subject which has developed this refractory state be immersed in fresh antiserum, they are still capable of being dissolved, but not capable of being so destroyed if there is added to the mixture some of the subject's own serum.

Vidal has found that action of this antisensibilizing substance can be set aside both *in vitro* and *in vivo* by the use of an antiserum prepared from effusions of such refractory patients. The rarity, however, of such effusions makes such a method of treatment difficult. When once obtained, however, these sera neutralize the antisensibilizing substance and are of very great value for the reason that they are not specific for any special type of cancer. They will apply to

all cases of cancer treated by the cytolytic antiserum obtained from the dog to which a refractory state may have developed.

Vidal has treated 94 cases of cancer during the past ten years in the development of these principles, and as a result of this work draws the following conclusions: If there is a possibility of employing an antiserum upon any patient the rejection of such a patient, no matter how late the case, is never justified, and, however impossible it may seem, the value of the method of treatment is real.

Of the 94 cases which Vidal has treated, 3 received no other treatment and are as follows: 1. An epithelioma of the tongue, verified by a microscopic examination, and of considerable size. Received 46 injections in seven months' time and 10 injections during two years following. Patient healed and living seven years. 2. A cylindrical epithelioma of the rectum; operation refused, and diagnosis verified by the microscope; 25 injections in one year and 13 during the next year. Well thirteen years after. 3. Epithelioma of the breast, ulcerated and inoperable; confirmed by a microscopic examination. Patient received 70 injections; was well ten years later. There were 48 patients operated upon, and, on account of the difficulty of distinguishing in such cases how much to attribute to the operation and how much to the immunization, it may not be proper to include these cases in this series; nevertheless, 28 of these cases survived seven years,—a higher proportion, in the author's mind, than would likely have followed operative methods alone.

Twelve of the cases died untraced and 8 died of a fatal recurrence. Among these cases was one of cancer of the cervix which refused intervention under serum treatment. It disappeared after 60 injections and was well six years later. Another case was a sarcoma of the trapezius which had recurred. It disappeared under the serum therapy, and the patient was well five years later. A third case was a very advanced tumor of the breast. The patient received 45 injections, after which a partial absorption took place, permitting a local removal of the mass. Then a continuation of the serum therapy resulted in recovery, the patient remaining well for three years.

Of the remaining 45 cases 2 should be deducted, inasmuch as they were either too far advanced or treated too radically; 15 showed no improvement; 19 showed considerable improvement equivalent in some cases to temporary cure (two years),—from a subjective standpoint, nearly complete. In other cases the cure was only less marked and not as lasting.

These results have been confirmed to a certain degree by Beebe (*Med. Rec.*, lxxxii, ii, 1912) in this country. He has developed a cytolytic serum by injecting an animal with the cancer cells and then injecting the patient with increasing doses either intramuscularly or, better, intravenously.

It appears to the author that these results are very remarkable and demonstrate beyond doubt the existence of a true specific for cancer and a strong probability of the development of a successful method of sera treatment of cancer by its use. Very little need be said of the parasitic serum therapy. Tuffier, Le Toux and

Emerich and his school, and Whaef and San Felici have published some results which are far from being of the same order as those just described, comparing in efficiency rather with those obtained by the use of normal blood-serum.

Cancer, then, represents various forms of misbehavior of the normal tissue-cells of the body, is not caused by a parasite, and as yet has not, and perhaps never can have, any one means of cure. Until we know more of the ultimate causes which lead certain cells to take on what we call malignancy, manifested by exuberant growth with a tendency to invade and destroy other tissues, we cannot formulate any intelligent plan of medical treatment; although the observations of many seem to show that faulty nitrogenous metabolism may have something to do with it, and indicate that more studies should be made along the lines of animal chemistry. Nor are there any remedies with much specific action on cancer. The various local measures mentioned all have their limitations, and radiant energy, even, cannot accomplish more than a certain amount of good.

Thus far surgery offers the best percentage of results along certain lines, and modern surgery has vastly improved this percentage over that of fifty years ago. But even surgery has its limits when the disease has progressed beyond a certain stage, and not infrequently it seems unable to check the ravages of cancer at any stage.

The lesson to be learned, however, is, just when the knife must be resorted to. The surgeons say, very properly, the earlier, the better, and plead for the immediate removal of even suspicious tumors; unquestionably far more harm results from delaying too long before

resorting to operation than from operating too early. The judgment of the physician, therefore, should ever be free and unbiased, and the claims put forth in favor of this or that method of treatment should not cloud the judgment of the physician or patient as to the proper claims of surgery, nor should operative interference be delayed until the chances of cure offered by surgical procedure are lessened beyond reasonable hope.

Good surgery should promise 100 per cent. of cures in all cases in which the carcinoma is still a local growth. The figures, 50 per cent. inoperable and 50 per cent. cured of the operable, giving about 25 per cent. of cures, vary to a slight degree with cancer in different regions, and with different types of cancer in the same region. It is a question whether had surgery ever cured a case. We should try to educate the public to get this good surgery at once, when it promises most. Delay after the first warning is dangerous. Trifling with any other treatment is gambling with death; and physicians are often responsible for such procrastination and trial of doubtful methods of treatment. J. C. Bloodgood (So. Med. Jour., July, 1915).

The recent essential change in our views of cancer is an acceptance of the modern idea that the duty of the physician to his patients is now to recognize, diagnose, and treat radically the conditions which ordinarily *precede* cancer. The general principle is immediate removal of any mechanical or physiological irritation which could conceivably cause an existing thickening or ulceration, and if this is not followed by prompt disappearance of the lesion, an immediate and thorough excision of the induration or ulcer while still benign. Radiation and the cautery should be avoided during the early stages, though of great value in the palliation of advanced disease. The following are

pre-cancerous conditions which are not malignant: Moles (especially pigmented), keratoses, ulcers of skin and orifices, gallstones, ulcers of stomach, ulcers of mouth, cystitis, erosions of cervix, premature or obstructed involution of breast, uterus, or prostate, the adenomata, the papillomata. Cysts in the ovary and breast (because they tend to develop papillomata of their linings), polyps of uterus or rectum, and, in general, all epithelial neoplasms.

In squamous epitheliomata of the surface and carcinomata originating in the follicles of the skin, radiation, cauterizing agents or freezing mixtures may be employed in the early stages; if any suspicion of malignancy arises, however, they should be radically removed together with the nearest set of lymphatic glands. Any chronic lump in the breast

which has persisted for a month without decrease should be removed. E. Reynolds (Boston Med. and Surg. Jour., Aug. 1, 1918).

Prompt and durable relief of the unbearable neuralgic pains accompanying extensive pelvic cancer is afforded by intraspinal injection of 2 c.c. (32 minims) of a 10 per cent. solution of **quinine and urea hydrochloride**. During the 12 days to date of writing the relief from pains had been so great that morphine had not been required. Before this the woman had required repeated injections of morphine. The intraspinal injection induced a transient febrile reaction, with headache and vomiting, but there were no motor or vasomotor by-effects. B. Fortacin (Revista de Med. y Cir. Pract., Jan. 21, 1919).

H. H. JANEWAY,
New York.

